Pharmacokinetics and Pharmacogenomics: Clinical Implications

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The 4 Phases of Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacokinetics

Absorption

- Pharmaceutical Factors
  - Rate of dissolution
  - Lipid solubility
  - Route
- Clinician/Patient Factors
  - Surface area
  - Blood flow
  - Route
  - Competition

Absorption

- The liberation phase extends from the time of drug administration to the point where the drug is dissolved in body fluids and ready for absorption. Absorption is the process of drug movement from the absorption site across one or more cell membrane barriers into the circulation.
- The most common mechanism for drug absorption is PASSIVE DIFFUSION.

Physiologic Factors Affecting Absorption

- First-pass effect (presystemic metabolism)
- During the process of drug absorption from the gastrointestinal (GI) tract, there are two potential sites for metabolism of the drug to occur: 1) gut wall, and 2) liver. If the drug is metabolized (chemically altered) as it passes through either of these sites, it is said to undergo first-pass metabolism. Effectively, the drug has been metabolized before it ever reaches the systemic circulation.
Physiologic Factors Affecting Absorption

• First-pass effect (presystemic metabolism)
• Some drugs are so extensively metabolized when taken orally that therapeutic effects cannot be obtained, e.g., lidocaine. These drugs must be given by injection. Other drugs must be given in very large doses orally, compared to parenteral doses, to achieve therapeutic effects; e.g., propranolol per os (PO) 10 to 30 mg every six to eight hours (antihypertensive), intravenous 1 to 3 mg (antiarrhythmic).

Pharmacokinetic Factors Affecting Absorption

• Elevation of gastric pH by antacids
  – Increases the absorbance of basic drugs; decreases that of acidic drugs
• Laxatives
  – Increase peristalsis and decrease GI transit time
• Drugs that are constipating may increase absorption of other meds
• Adsorbents
• Drugs that decrease GI blood flow

Clinical Relevance—Absorption

• May change over the lifespan
• Presystemic metabolism is considered when drugs are developed.
• Highly route dependent
• Via the PO route, make sure the patient is aware of the “empty stomach” rule, AND that it applies to antacids, anti-diarrheals

Distribution

• Blood flow to tissues
• Barriers to distribution
  – Blood brain barrier
  – Placenta
• Protein binding

Factors Determining Drug Distribution

1. Blood flow to tissues (perfusion)
   – Rapidly perfused tissues, such as the heart, liver, kidney, brain, and lung, are exposed to the drug in the first few minutes following absorption (initial phase of drug distribution). Less rapidly perfused tissues (muscle and skin) and poorly perfused tissues (bone and fat) are exposed to the drug as the drug reaches its final distribution pattern over a period of hours.

Factors Determining Drug Distribution

2. Binding of drug to plasma protein
   – reversible (noncovalent bonding)
   – free drug + protein <----- drug-protein complex
     • albumin (binds acidic drugs)
     • alpha-1 acid glycoprotein (binds basic drugs)
     • lipoproteins
Factors Determining Drug Distribution

2. Binding of drug to plasma protein
   - Only free drug can diffuse to the site of action. Pharmacologic activity depends on free drug concentration in plasma for very highly bound drugs.
   - Reservoir effect may prolong both the duration of drug action and half-life.
   - There may be excess free drug present if hypoalbuminemia occurs and resulting toxicity; important only for highly bound drugs, may require dosing adjustment.

Factors Determining Drug Distribution

3. Specialized distribution barriers
   - Blood-brain barrier (BBB)
     - No intercellular pores between brain capillary endothelial membranes due to the presence of tight junctions between cells.
     - Effects—severe limitation on movement of ionized or highly polar species; these substances cannot easily penetrate the BBB.
     - For drugs to gain access to the brain from the capillaries, drugs must diffuse across cells (lipid-soluble, nonionized form) or be actively transported by a carrier.

The Blood Brain Barrier

Factors Determining Drug Distribution

3. Specialized distribution barriers
   - Placental Barrier
     - Drugs cross placenta by diffusion; lipid-soluble, nonionized drugs penetrate most rapidly.
     - Usually, placental transfer of drugs is relatively slow, with the equilibration time between maternal blood and fetal tissues estimated at about 15 minutes for some drugs and almost an hour for other drugs.

Factors Determining Drug Distribution

3. Specialized distribution barriers
   - Placental Barrier
     - Virtually every drug used for therapeutic purposes can and does cross the placenta; effectively, no real barrier exists. In addition, many illicit drugs and other toxic substances absorbed by the mother will gain exposure to the fetus. Drugs are classified on a scale (A, B, C, D, X) for safety for use in pregnancy based on their ability to harm the fetus.

Factors Determining Drug Distribution

Linkage of Fetal and Maternal Blood Supplies via the Placenta
Development of Placenta

Pharmacokinetic Factors Affecting Distribution
- Competition for protein binding sites
  - Occasionally significant
- Alteration of extracellular pH
  - Useful in cases of overdose, poisoning, etc.
  - Can alkalize the urine to excrete acidic drugs

Clinical Relevance—Distribution
- Clinical Significance
- Very relevant in your sickest patients
- Blood flow is the determinant here, so always consider distribution disturbances in the patient with cardiovascular disease, vessel disease, perfusion disorders
- Remember barriers

Metabolism—Purposes
- Detoxification (defense) mechanism
  - Chemical conversion of a toxic substance to a less toxic metabolite for termination of drug action
  - Chemical conversion of a pharmacologically active substance to an inactive metabolite

Metabolism
- Conversion of a relatively lipid-soluble parent drug molecule to a much more polar, water-soluble drug metabolite which can be readily excreted.
- The more lipid-soluble parent form of the drug is not easily eliminated by the body’s excretory mechanisms (renal and biliary excretion).
- Drug metabolism produces a polar, water-soluble substance which is more easily excreted from the body.
- There is individual variation in metabolism—pharmacogenetics.

Sites for Drug Metabolism
- Liver - smooth endoplasmic reticulum in hepatocytes contain many drug-metabolizing enzymes; some enzymes are found in cytosol.
- Gut wall and mucosal surface
- Plasma
Types of Metabolic Reactions

- **Phase I** (nonsynthetic) - major types
  - Oxidation by the cytochrome P450 system which is a family of drug-metabolizing enzymes in the liver. The major function of this enzyme system is to add an oxygen atom to the drug substrate.
  - \( \text{drug} + \text{O}_2 \rightarrow \text{drug-OH} \)  
    
    (nonpolar, lipid-soluble) \( \rightarrow \) (polar, water-soluble)

Metabolism

- Cytochrome P450 enzyme system
  - CYP1, CYP2, CYP3
  - Families of enzymes that metabolize drugs
  - Nine other CYPs that metabolize endogenous compounds in the body
  - Divided further into subclasses designating isoforms that metabolize specific drugs/drug families

Phase I Metabolism

- CYP2D6

Classes of CYP450

Types of Metabolic Reactions

- **Phase II** (synthetic) reactions occur in the liver and gut wall. The products of Phase II reactions are called conjugated metabolites and are virtually always inactive, very polar and/or ionized, and easily excreted. Several types of conjugation may occur, including:
  - Glucuronide conjugation - liver
  - N-acetylation - liver, gut wall; addition of an acetate group to a nitrogen atom. Individuals are classified as either slow or fast acetylators depending on genetic factors, e.g., sulfonamides, isoniazid, procainamide.

Acetaminophen Glucuronidation
Considerations of Metabolism

- Age
- Induction
- Inhibition
- First-pass effect
- Nutritional status
- Disease state
- Enterohepatic circulation

Enterohepatic Circulation

- Enterohepatic circulation - steps
  I. Secretion of a substance (drug, drug metabolite, or other foreign chemical) with bile into the small intestine
  II. The substance is reabsorbed from the small intestine back into the mesenteric blood draining the GI tract
  III. The substance is carried in the portal blood back to the liver where it may again be secreted into bile

Enterohepatic Circulation

- Enterohepatic circulation - steps
  I. This enterohepatic cycling (movement between the liver and small intestine) may greatly prolong the drug's persistence in the body. Ultimately, the substance is renally or fecally excreted.
  II. Only drugs that are glucuronidated undergo this step

Pharmacokinetic Factors Affecting Metabolism

- Induction of the CYP isoenzymes
  - Phenobarbital, phenytoin, carbamazepine, rifampin, ethosuximide, alcohol, tobacco, etc., etc.
- Inhibition of CYP isoenzymes
  - Acyclovir, isoniazid, OCP, fluoxetine, cimetidine, erythromycin, etc., etc.

Drugs Affected by Grapefruit Juice

- Statins: Lovastatin (Mevacor), atorvastatin (Lipitor), simvastatin (Zocor, Vytorin)
- Antihistamines: Ebastine
- Calcium channel blockers: Felodipine (Nitrendipine, Plendil), nifedipine (Adalat, Procardia), nicardipine, nimodipine, and nisoldipine
- Psychiatric drugs: Buspirone (Buspar), triazolam (Halcion), carbamazepine (Tegretol), diazepam (Valium), midazolam (Versed), sertraline (Zoloft), fluoxetine (Prozac), fluvoxamine, and pimozide (Orap)

Pharmacokinetic Factors Affecting Metabolism

- Genetics
- Food—grapefruit juice
  - Effects GI CYP3A isozyme decreasing intestinal metabolism of many drugs
  - Effects persist up to 3 days after last glass of juice!
Drugs Affected by Grapefruit Juice

- Immune suppressants: Cyclosporine (Neoral), tacrolimus (Prograf)
- Pain medications: Methadone
- Erectile dysfunction med: Sildenafil (Viagra)
- Anti-retroviral: Aquinavir (Invirase)
- Antiarrhythmics: Amiodarone (Cordarone)
- Caffeine

Clinical Relevance—Metabolism

- Cannot be overstated!
- Determines dose
- Determines effect
- Influences ADRs
- Is influenced by disease processes which affect the liver and gut primarily
- Has a major genetic component
  - Pharmacogenomics

Excretion

- Renal excretion of drugs is the primary way to get drugs out of the body.
- What is the proper measure of renal function?
- Does it change over time?
  - Renal function decreases by 10% with each decade after the 40’s. Adjustments may need to be made in drug dosing in elderly patients

Excretion—Major Routes

- Kidney
- Bile (followed by fecal excretion)
- Pulmonary
- Breast milk
- Saliva (swallowed, reabsorbed)

Excretion—Principles

- A drug may be excreted either as unchanged parent drug (if it is sufficiently polar) or as a metabolite
- Lipid-soluble compounds are not easily excreted and must be metabolized to more polar, water-soluble substances

Excretion

- Although drugs can gain access to the urine via glomerular filtration, most drugs are put in the urine by active tubular secretion. This allows for large, charged drug molecules to be added to the urine for excretion from the body.
Active Tubular Secretion

**Pharmacokinetic Factors Affecting Excretion**

- Altered renal excretion due to drug-induced decreased cardiac output
- Drug-induced changes in urinary pH
- Competition for active tubular secretion sites
- P-Glycoprotein
  - A transmembrane protein that transports drugs out of cells; may be induced or inhibited
  - When induced, see decreased absorption, decreased fetal drug exposure, decreased brain/CNS drug exposure, increased drug elimination

P-Glycoprotein

**Clinical Relevance—Excretion**

- Implications increase at the extremes of age and in disease states
  - Dosage and effects/ADRs are affected
- Genetics may also play a role as we learn more about P-glycoproteins
- Highly linked to metabolism for most drugs....

Other Factors to Consider

- **Body Weight**
  - Body surface area is more precise.
- **Age**
  - Extremes of age most vulnerable
- **Tolerance**
  - Metabolic, pharmacodynamic, tachyphylaxis
- **Placebo effect**
- **Gender**

Gender Effects

- This is an area we know little about...for now!
- In 1997, the FDA ordered the inclusion of more females in drug tests—especially for drugs to treat life-threatening conditions.
- We know that:
  - Digoxin may increase mortality in women.
  - Alcohol is metabolized more slowly by women.
  - Pentazocine and nalbuphine work in lower doses in women than in men.
  - Quinidine is more likely to cause Torsades de pointes in women than in men.
Drug Use in Pregnancy

- Teratogens may cause gross malformations in the first trimester—some not compatible with life.
- In the second and third trimesters, teratogens often cause functional disturbances (i.e., renal, CNS, heart).
- FDA has drugs ranked A,B,C,D,X.

Drugs to Avoid in Pregnancy

- Antiseizure Drugs
  - Carbamazepine, valproic acid, phenytoin, etc.
- Antibiotics
  - Nitrofurantoin, sulfonamides, tetracyclines
- Angiotensin-converting-enzyme inhibitor, angiotensin receptor blockers
- Lithium
- NSAIDs
- Warfarin
- Oral hypoglycemics
- PTU, Methimazole

Pediatric Populations

- Most pharmacokinetic parameters are different here—especially early.
  - Absorption may not normalize until about age two.
  - Plasma proteins are lower for the first year, so distribution of drugs may be affected.
  - BBB not fully developed in infants, so CNS is sensitive.
  - Metabolic enzymes do not fully develop until about a year.
  - Renal function approaches adult levels at about a year.

Geriatric Populations

- Many pharmacokinetic changes related to organ failure
  - Absorption is decreased slightly.
  - Distribution is affected by increased body fat, less lean body mass, decreased total body weight, and decreased serum albumin.
  - Slight decrease in hepatic metabolism
  - Progressive decline in renal function and resulting drug accumulation is the MOST common cause of ADRs in the elderly!
  - Monitor with CrCl

Other Factors to Consider

- Polypharmacy
- Multiple illnesses that are severe or chronic
- Compliance
- The Beers list offers the updated “drugs to avoid” in the elderly—or at least ones which are most likely to cause the greatest ADRs.

Race/Ethnicity

- Based on the African-American Heart Failure Trial, BiDil (ISDN and hydralazine) was approved for African Americans with heart failure. By seeking patent approval this way, the drug company was able to get LONGER patent approval.
- Drugs for asthma and other cardiovascular concerns are now being marketed this way as well...
- Pharmacogenetics may be an indicator for some race-related drug sensitivities.
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**The Interplay of Pharmacokinetic Factors**

**PHARMACOGENOMICS**

**Pharmacogenomics—What is it?**

- The study of how genetic variations affect individual responses to drugs
- Impacts therapeutic effects
- Impacts adverse effects
- Clinically relevant for several drugs thus far, though testing is required for only a few

**Impact of Genetics**

- May account for 20% to 95% of variability of drug responses
  - One study showed incorrect doses accounted for 42% of adverse effects; genetics accounted for 50%.
  - CYP450 polymorphism explains variability in drug response.
  - Genetic polymorphism is included in FDA labeling.

**Genotyping for All?**

- AmpliChip CYP450 test can detect many CYP2D6 and CYP2C19 polymorphisms.
  - These metabolize 25% of all drugs such as beta blockers, antidepressants, analgesics, anticonvulsants, benzodiazepines, and proton-pump inhibitors.
  - The test can predict, but not confirm, metabolizing status.
  - Pharmacogenetic tests exist for voriconazole, atemoxetine, irinotecan, clopidogrel, warfarin, etc., etc.—these predict an increased tendency for adverse effects.

**Genetic Testing Required...**

- Cetuximab
- Trastuzumab
- Maraviroc
- Dasatinib
- Recommended for carbamazepine, valproic acid, mercaptopurine
Genetic Testing for Drug Response

- Maraviroc (Selzentry)—used for CCR5-tropic HIV-1 strains, to suppress viral load and restore immune function. The patient MUST BE tested for CCR5-tropic HIV prior to use.
- Trastuzumab (Herceptin)—used for breast cancer and metastatic gastric cancer. The patient MUST BE tested for HER2.

Genetic Testing for Drug Response

- Cetuximab (Erbitux) - indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. Erbitux, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens.

Genetic Testing for Drug Response

- Dasatinib (Sprycel)– indicated for newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. The trial is ongoing and further data will be required to determine long-term outcome.

Genetic Testing for Drug Response

- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

Genetic Testing Recommended

- Warfarin or clopidogrel
- Carbamazepine
- Why?
  - Recommended due to therapeutic/adverse effects
  - But only recommended….due to cost!

Clopidogrel

- Needs to be metabolized to its active thiol intermediate—this explains inter-patient sensitivity.
- Metabolism is accomplished by the CYP3A4, CYP3A5 and CYP2C19 isoenzymes.
  - CYP2C19 is thought to contribute most to patient variability in response
Warfarin

- CYP2C9 test and the VKORC1 test
- Vitamin K epoxide reductase complex subunit 1
- IWPC Pharmacogenetic Dosing Algorithm
- Examples: Patients who carry the *2 mutation are slower metabolizers of warfarin by 30% (11% of population); those who have the *3 allele metabolize it 80% slower (7% of population), so dosage adjustments need to be made or adverse effects will be seen. Patients with mutations in VKORC1 need 20% less warfarin (40% of pop).

Recommended Daily Warfarin Doses to Achieve Therapeutic INR Based on Genotype

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How to Determine if a Genetic Test is Appropriate for a Patient?

- Is the drug appropriate?
- Could a different drug be substituted?
  - Especially one that does not require testing?
- Is the genetic test available and valid (and affordable)?
- Are the results of the test clinically relevant to the medical team?
- What is the turnaround time for the test?

SUMMARY

- ADME considerations are always important in safely prescribing
  - Especially in extremes of age
  - In the patient who has hepatic and/or renal disease
- Pharmacogenomics are asserting themselves!
  - A few genetic tests are available and are relevant.
  - But always consider the patient factors of importance

SUMMARY

- Is testing necessary?
- Is another drug available that would make testing irrelevant?
- Is the test going to tell the NP or the medical team anything essential?
- Always consider time and money—both yours and the patient’s!
- Stay tuned for pharmacogenomic impact of drugs
  - Watch for FDA statements as they become available