Variation in drug responses

&

Drug-Drug Interactions
Properties of an Ideal Drug

Effective
Safety
Selective
Reversible Action
Predictable
Freedom from drug interactions
Low cost
Chemically stable
Sources of Variability in Therapeutic Responses

Similar drugs usually produce similar qualities of responses in patients, but might produce different intensities and duration of effects.

- Dose, Dosage schedule, and Route of administration.
- Diurnal variation ”Chronopharmacology”.
- Age and sex of the patient.
- Drug reactions.
- Drug interactions: other drugs, diet, and environment.
- Placebo effect.
- Intercurrent illnesses.
- Tolerance.
- Genetic or racial factors, “Pharmacogenetics”.
Causes of Variability in Drug Response

Those related to the biological system
1. Body weight and size
2. Age and Sex
3. Genetics - pharmacogenetics
4. Condition of health
5. Placebo effect
Causes of Variability in Drug Response

• Those related to the conditions of administration
  1. Dose, formulation, route of administration.
  2. Resulting from repeated administration of drug:
      drug resistance; drug tolerance-tachyphylaxis; drug allergy
  3. Drug interactions:
      chemical or physical;
      GI absorption;
      protein binding/distribution;
      metabolism (stimulation/inhibition);
      excretion (pH/transport processes);
      receptor (potentiation/antagonism);
      changes in pH or electrolytes.
Pharmacogenomics:  
The relation between the individual’s genetic makeup to his/her response to specific drugs (entire genome).

Pharmacogenetics:  
Interindividual variation in drug response that is due to genetic influences (specific gene).
Metabolism

• The liver is the major side of metabolism for many drugs, but other organs, such as lungs and kidney can also metabolize drugs.

• Many lipid soluble drugs are not readily eliminated from the body and must be conjugated or metabolized to compounds that are more polar and less lipid soluble before being excreted.

• Metabolism often, but not always, results in inactivation of the compounds.

• Some drugs are activated by metabolism, these substances called prodrugs.
Phase I metabolism

• Drug metabolism occur in two phases:

• Phase I reactions function (e.g., oxidation, reduction, hydrolysis) alter chemical reactivity and increase water solubility.

• Phase I reaction frequently catalysis by the cytochrome P450 system (also called microsomal mixed function oxidase).

\[
\text{Drug } + \text{O}_2 + \text{NADPH} + \text{H}^+ \rightarrow \text{Drug}_{\text{modified}} + \text{H}_2\text{O} + \text{NADP}^+
\]

• To date, 12 unique isoforms of this enzymatic system (CYP 2D6, CYP3A4) have been identified to play a role in human drug metabolism.
Phase II metabolism

• If the metabolite from phase I is polar enough it will be excreted by the kidney, but if it is still lipophilic to be retained in the kidney, a subsequent Phase II metabolism will take place.

• Phase II consists of conjugation reaction with endogenous substances, such as, glucuronic acid, sulfuric acid, or an amino acid.

• Results in polar and usually more water soluble compounds.
1. Poor metabolizer (PM)
   - has low metabolic capacity
   - has two mutant alleles

2. Intermediate metabolizer (IM)
   - has metabolic capacity between PM and EM
   - has one reduced activity allele and one null

3. Extensive metabolizer (EM)
   - has regular metabolic capacity
   - has at least one and no more than two normal functioning alleles

4. Ultrarapid metabolizer (UM)
   - has higher metabolic capacity than EM
   - has multiple copies of functional alleles
Cytochrome P450 system

- Cytochrome P450 system dependent enzymes are important target for drug interaction because they can be induced or inhibited by certain drugs.

- Cytochrome enzymes. Inducers like rifampin and carbamazepine are capable of increasing the synthesis of one or more of isoforms. For example, Rifampin significantly decreases the plasma concentration of HIV protease inhibitors.

- Cytochrome enzymes inhibitors, Omeprazole inhibits three CYP isoforms that are responsible for warfarin metabolism, leading in an elevation in the warfarin concentration, and so greater inhibition of coagulation, leading in to more risk of serious bleeding reaction,
Drug-drug interaction

- When two drugs taken together, there is a possibility that the drugs will interact with each other to cause unanticipated effect. Usually increase or decrease in the desired therapeutic effect.

- Drug-drug interaction can occur in the following sites

1. at the side of absorption, tetracycline is not absorbed from the GI tract if calcium product present in the stomach.

2. during biotransformation (CYP 450).

3. At the site of action, drug antagonism.
Drug-drug interaction

3. During excretion, digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.

4. During distribution, aspirin competes with methotrexate for protein binding sites, and because aspirin is more competitive for the sites, resulting in increased release of methotrexate and so increase toxicity to tissues.
Adverse effect

- Adverse effect are undesired effect that may be unpleasant or even dangerous they can occur for many reasons:
  1. The drug may have other effects on the body besides the therapeutic effect.
  2. The patient is sensitive to the drug.
  3. The patient is taking too much or too little of the drug.

- the nurse, as the most frequently administers medications, must be constantly alert for sign of drug reactions of various types.
Remember !!!

• With every drug use, unwanted effects must be taken into account.
• Before prescribing a drug, the physician should therefore assess the risk: benefit ratio.
• In this, knowledge of principal and adverse effects is a prerequisite.
A. Adverse drug effect: overdosing

B. Adverse drug effect: increased sensitivity
Adverse Drug Reaction

- Adverse drug reactions are classified as predictable or unpredictable.
- A predictable drug reaction is related to the pharmacological actions of the drug.
- An unpredictable reaction is related to immunological response (hypersensitivity reactions) or non-immunological response.
Drug Allergy

• It is defined as an adverse reaction to a drug by a specific immune response either directly to the drug or one or more of its metabolites alone, or to a drug bound to a body protein such as albumin, (Hapten).

• Such binding alters the structure of the drug/protein complex, rendering it antigenic.
Reaction of immune system to first drug exposure

Drug (= hapten)
Protein
Macromolecule MW > 10 000
Antigen

Immune system (= lymphatic tissue) recognizes:
"Non-self"

Production of antibodies (Immunoglobulins) e.g. IgE, IgG etc.
Proliferation of antigen-specific lymphocytes

Distribution in body
## Classification of Allergic Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Time</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Anaphylactic</td>
<td>sec/min</td>
<td>Angioedema</td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic</td>
<td>--</td>
<td>Transfusion rx</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex</td>
<td>6-8hrs</td>
<td>Serum sickness complex</td>
</tr>
<tr>
<td>IV</td>
<td>Cell mediated</td>
<td>48 hrs</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>
Immune reaction with repeated drug exposure

**Type 1 reaction:**
- Acute anaphylactic reaction
- Urticaria, asthma, shock
- IgE
- Receptor for IgE
- Histamine and other mediators

**Type 2 reaction:**
- Cytotoxic reaction
- IgG
- Complement activation
- Membrane injury
- Cell destruction

**Type 3 reaction:**
- Immune complex
- Deposition on vessel wall
- Activation of complement and neutrophils
- Inflammatory reaction

**Type 4 reaction:**
- Lymphocytic delayed reaction
- Contact dermatitis
- Antigen-specific T-lymphocyte
- Inflammatory reaction
- Lymphokines
Compliance

Time course of drug concentration with irregular intake
Adults >65 years old

• growing population

• 20% of hospitalizations for those >65 are due to medications they’re taking
Pharmacokinetics

• Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution

• Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin
  – Serum levels may go up due to decreased volume of distribution

• Fat soluble: diazepam, thiopental, trazadone
  – Half life increased with increase in body fat
Oxidative metabolism through cytochrome P450 system does decrease with aging, resulting in a decreased clearance of drugs.
Pharmacokinetics: Excretion and Elimination

• GFR generally declines with aging, but is extremely variable
  • 30% have little change
  • 30% have moderate decrease
  • 30% have severe decrease

• Serum creatinine is an unreliable marker

• If accuracy needed, do Cr Cl
Example: Creatinine Clearance vs. Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Scr</th>
<th>CrCl</th>
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<tbody>
<tr>
<td>30</td>
<td>1.1</td>
<td>65</td>
</tr>
<tr>
<td>50</td>
<td>1.1</td>
<td>53</td>
</tr>
<tr>
<td>70</td>
<td>1.1</td>
<td>41</td>
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<tr>
<td>90</td>
<td>1.1</td>
<td>30</td>
</tr>
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</table>
Pharmacodynamics (PD)

• Definition: the time course and intensity of pharmacologic effect of a drug

• Age-related changes:
  – ↑ sensitivity to sedation and psychomotor impairment with benzodiazepines
  – ↑ level and duration of pain relief with narcotic agents
  – ↑ drowsiness and lateral sway with alcohol
  – ↓ HR response to beta-blockers
  – ↑ sensitivity to anti-cholinergic agents
  – ↑ cardiac sensitivity to digoxin
Factors contributing to adverse drug reactions in elderly patients

Polypharmacy

How many prescription medications are too many? >4 or >6
Many elderly people receive 12 medications per day

Multiple disease states

Multiple drug administration

Impaired organ function

Orthostatic hypotension, when they standup, blood goes to their feet - weak sympathetic nervous system response to constrict veins and increase heart rate. Low thyroid function causes lower body temperature, metabolic rate, & heart rate.

Heart, kidney, liver, thyroid

Decreased homeostatic regulation

Low thyroid function causes lower body temperature, metabolic rate, & heart rate.

Altered drug concentrations

Altered organ function

Adverse drug reaction

Altered compliance
Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
  - More available drug
- Immature liver/kidneys
  - Liver often metabolizes more slowly
  - Kidneys may excrete more slowly
Pediatric Dosing

Traditionally, for less frequently used drugs, extrapolation is done from adult dose on a weight or surface area basis.

Problems
- Absorption may be more or less than adult
- Clearance of some drugs in children is affected by maturation, as well as size
  - Cytochrome P450 enzyme system matures over time
  - Glomerular filtration changes over time
- Drug targets may vary with age
CYP Enzymes
• CYP isoforms vary with age
• For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life

• Carbamezapine (3A4) clearance faster in children than adults – requires higher doses
• “Children are not Small Adults”
Questions ??????