Variables Affecting Drug Actions & Special Populations

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Variables that Affect Drug Actions

1. Dosage
   - Includes amount and frequency
   - Too small of dose = not therapeutic
   - Too large of dose = toxic effects

2. Route of administration
   - Influence absorption & distribution

3. Drug-Diet interactions
4. Drug-Drug interactions
3. **Drug-Diet Interactions**
   - Food may slow absorption by slowing gastric emptying time
   - Food may form an insoluble compound
     - Ex: tetracycline & dairy products (tetracycline combines with calcium & forms unabsorbable compound)
   - Tyramine containing foods & MAO inhibitor
     - Causes release of norepinephrine & produces severe hypertension
   - Warfarin (Coumadin) and foods with vitamin K
     - Vitamin K (in green, leafy vegetables) antagonizes action of warfarin

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4. **Drug-Drug Interactions**
   - Interactions that can increase the therapeutic or adverse effects of drugs
     - **Additive effects**
       - 2 drugs with similar actions
       - Example: sedative drug + alcohol = increased sedation
     - **Synergism or potentiation**
       - 2 drugs with different mechanisms of action that produce greater effects when taken together
       - Example: acetaminophen + codeine = Tylenol #3 (greater analgesia)
Variables that Affect Drug Actions

4. **Drug-Drug Interactions**
   - Interactions that can increase the therapeutic or adverse effects of drugs
     - **Interference**
       - Interference by one drug with the metabolism or elimination of a 2nd drug results in increased effects of 2nd drug
       - **Example:** cimetidine (Tagamet) inhibits drug metabolizing enzymes in the liver (thus, decreased metabolism of many drugs such as benzodiazepines, beta-blockers, theophylline)
     - **Displacement**
       - Displacement of one drug from plasma protein binding sites by a 2nd drug = increased effects of displaced drug
       - **Example:** warfarin (Coumadin) + aspirin = increased anticoagulant effect of warfarin

Variables that Affect Drug Actions

4. **Drug-Drug Interactions**
   - Interactions in which drug effects are decreased
     - **Antidote**
       - Given to antagonize the toxic effects of another drug
       - **Example:** naloxone (Narcan)
     - **Decreased intestinal absorption**
       - When oral drugs combine to produce unabsorbable compounds
       - **Example:** antacids taken with tetracycline
Variables that Affect Drug Actions

4. **Drug-Drug Interactions**
   - Interactions in which **drug effects are decreased**
     - **Activation of drug-metabolizing enzymes in the liver**
       - Increases the metabolism rate of any drug metabolized primarily in the liver
       - **Example**: phenobarbital (enzyme “inducer”) + warfarin (Coumadin) = **decreased effect** of warfarin
     - **Example**: Sodium Bicarbonate (alkalinizes the urine) + phenobarbital = increased excretion of phenobarbital

Client-Related Variables

1. **Age**
   - Drug action most pronounced in pediatrics/geriatrics

2. **Body weight**
   - Recommended dosage targeted at 150 lb person

3. **Genetic & ethnic characteristics**
   - Patients have varied responses to a drug
     - May lack enzyme systems or overactive enzyme systems
     - Different metabolisms

4. **Pharmacogenetics**
   - Concerned with genetically related variability in responses to drugs
Client-Related Variables

5. **Pharmacoadthropyology**
   - Concerned with racial and ethnic differences in responses to drugs
   - **Example:** African Americans are less responsive to ACE inhibitors & beta-blockers

6. **Gender** (minor influence)
   - Males – more vascular muscles (effects seen sooner)
   - Females – more fat cells (drugs deposited in fat may be released slowly & cause effects for a prolonged period of time)

7. **Pathologic conditions**
   - All pharmacokinetic processes are decreased in CVD characterized by decreased blood flow to tissues
     - **Absorption**
       - of oral drugs decreased with vomiting & diarrhea
     - **Distribution**
       - altered in malnutrition, liver and vascular disease
     - **Metabolism**
       - decreased in malnutrition & liver disease
       - increased with hyperthyroidism & fever
     - **Excretion**
       - decreased in renal disease
Client-Related Variables

8. Psychological considerations
   - "placebo effect" – drug is more likely to be effective if patient thinks it will work

   - Personality influences – drug compliance (feel no control over health vs feel can influence health)

Drug Therapy in Pediatrics

1. Drug therapy must be guided by child’s age, weight, and level of growth & development

2. Choice of drug is often restricted (most drugs not sufficiently investigated in children)

3. Safe therapeutic dosage ranges are less well defined

4. PO when possible

5. IM in infants – should use thigh muscle (deltoid too small; gluteal muscles not developed until walking)

6. Keep all meds:
   - In childproof containers
   - Out of reach of children
   - Do NOT refer to as “candy”
Drug Therapy in Pediatrics

Physiologic characteristics and pharmacokinetic consequences

A. Increase in thinness and permeability of skin
   ► Increased absorption of topical drugs

B. Immature blood-brain barrier
   ► Increased distribution of drugs into CNS

C. Increased percentage of body water
   ► Increased volume of distribution

D. Altered protein binding until 1 year of age
   ► Greater amount of unbound (ACTIVE) drug due to decreased plasma proteins available for drug binding

E. Decreased glomerular filtration rate (kidney function mature by 1 year of age)
   ► Slowed excretion; may need to decrease the dose

F. Decreased activity of liver drug-metabolizing enzyme systems in neonates & infants
   ► Slowed metabolism
   ► Reaches adult levels by 6 months

G. Increase activity of liver drug-metabolizing enzyme systems in children
   ► Rapid metabolism (ages 1-4 yo)
   ► At puberty, decreases to adult level
   ► Monitor!
Medication Use During Pregnancy

- What is the teratogenic risk?
  - Teratogen = a substance that has the potential to create a characteristic set of malformations in the fetus.

- The teratogenic period?
  - Occurs in a specific time of fetal development, usually between day 31 and day 81 following the last menstrual period (LMP) when organogenesis is taking place.

- For a teratogen to exert its effect, it must be taken at the point in the pregnancy when the affected organ system is developing.

Stages of Human Development
Other Non-Teratogenic Effects

- Preterm labor risk?
- Birth weight?
- Other effects that are not clearly visible at birth?

Drug Properties in Pregnancy & Lactation

- Higher the MW = the more difficult passage
  - $\geq 1000$ Daltons = virtually no passage
  - Example: insulin

- 500 – 1000 Da = difficult passage

- 250-500 Da = easily passed
  - The majority of clinically useful drugs
  - The lower, the easier
  - Example: alcohol, nicotine, cocaine = $< 200$ Da
Drug Properties in Pregnancy & Lactation

- **Lipophilic** easier than hydrophilic
  - Placenta
  - Mammary alveolar tissue
  - Blood-brain barrier

### FDA Pregnancy Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Generally acceptable</td>
<td>Controlled studies in pregnant women show no evidence of fetal risk.</td>
</tr>
<tr>
<td>B</td>
<td>May be acceptable</td>
<td>Either animal studies show no risk but human studies not available or animal showed minor risks and human studies were done and showed no risk.</td>
</tr>
<tr>
<td>C</td>
<td>Use with caution if benefits outweigh risks</td>
<td>Animal studies show risk and human studies not available or neither animal nor human studies were done.</td>
</tr>
<tr>
<td>D</td>
<td>Use in life-threatening emergencies when no safer drug is available</td>
<td>Positive evidence of human fetal risk.</td>
</tr>
<tr>
<td>X</td>
<td>Do not use in pregnancy</td>
<td>Risks involved outweigh potential benefits. Safer alternatives exist.</td>
</tr>
</tbody>
</table>
# FDA Pregnancy Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Awesome</td>
<td>vitamins at recommended doses, levothyroxine (Synthroid)</td>
<td></td>
</tr>
<tr>
<td>B Best</td>
<td>penicillins, cephalosporins, azithromycin, erythromycin, acetaminophen, ibuprofen (caution at end of pregnancy in high doses)</td>
<td></td>
</tr>
<tr>
<td>C Caution</td>
<td>clarithromycin, ciprofloxacin, SSRIs, atypical antidepressants</td>
<td></td>
</tr>
<tr>
<td>D Danger</td>
<td>ACE inhibitors (&quot;pril&quot;), ARBs (&quot;sartan&quot;), doxycycline, carbamazepine (Tegretol), valproic acid (Depakote), lithium, paroxetine (Paxil - cardiac defects)</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>isotretinoin (Accutane), &quot;statins&quot; (decrease cholesterol), thalidomide</td>
<td></td>
</tr>
</tbody>
</table>

![FDA Pregnancy Risk Categories Diagram](image-url)
Hale’s Lactation Risk Categories

Lactation Risk Categories
L1: Safest
L2: Safer
L3: Moderately safe
L4: Possibly hazardous
L5: Contraindicated


Drug Therapy in Geriatrics

1. Physiologic age (ie, organ function) is more important than chronologic age

2. Difficult to separate the effects of aging from the effects of disease processes or drug therapy

3. Medications (prescription and OTC) should be taken only when necessary

4. Review current meds (including OTC and herbal therapy) before prescribing new drugs
5. Choice of drug should be based on available drug info regarding the elderly
   - Beer’s Criteria for Potentially Inappropriate Medication Use in Older Adults
     - guideline to help improve the safety of prescribing medications for older adults
   - Avoid medications with systemic **anticholinergic effects**:
     - Can’t see (vision changes)
     - Can’t pee (urinary retention)
     - Can’t spit (dry mouth)
     - Can’t ...poop! (constipation)
     - Example: first generation antihistamines (diphenhydramine – Benadryl)

**Anticholinergic Effects**

- Blind as a bat (vision changes)
- Red as a beet (flushing)
- Dry as a bone (dry mouth)
- Mad as a hatter (confusion)
- Hot as a hare (hyperthermia)
Drug Therapy in Geriatrics

6. Give smallest effective number of drugs

7. Give for the shortest effective time & smallest number of effective doses

8. When you have multiple choices in a drug class, choose a product with a shorter half-life

9. When new drug is started, the dosage generally should be smaller than for younger adults. Increments should be smaller and made at longer intervals.

   START LOW and GO SLOW!

10. Use nondrug measures when possible

11. Long-term therapy at home:
   - Large lettering for drug labels
   - Magnifying glass
   - Be sure client can open drug containers
   - Written schedules/drug containers for scheduling drug doses
   - Enlist family and friends

12. When client develops new symptoms, consider possibility of adverse drug effects
Drug Therapy in Geriatrics

Physiologic characteristics and pharmacokinetic consequences

A. Decreased GI secretions and motility
   ▶ Slower absorption and delayed onset of action

B. Decreased CO
   ▶ Slower absorption and distribution

C. Decreased total body water
   ▶ Water –soluble drugs distributed to smaller area (increased plasma concentration & risk toxicity)

D. Increased body fat
   ▶ Fat-soluble drugs distributed to larger area (longer duration of action)

Drug Therapy in Geriatrics

Physiologic characteristics and pharmacokinetic consequences

E. Decreased serum albumin
   ▶ Decreased protein binding; increased free, ACTIVE drugs

F. Decreased blood flow to liver
   ▶ Decreased drug metabolizing enzymes
   ▶ May increase half-life; prolonged responses

G. Decreased blood flow to kidneys
   ▶ Decreased glomerular filtration
   ▶ Drug accumulation
   ▶ Creatinine clearance to assess renal function
   ▶ May require dosage adjustments
Creatinine Clearance

Defining some terms:

- **Creatinine** – breakdown product of muscle creatine phosphate and is usually produced at a fairly constant rate by the body (depending on muscle mass)

- **Glomerular filtration rate (GFR)** – volume of fluid filtered from the renal glomerular capillaries into Bowman’s capsule per unit time

- **Creatinine clearance (CrCl)** – a comparison of the level of urine creatinine with blood creatinine. Because creatinine is found in stable plasma concentrations, is freely filtered and is not reabsorbed, and is minimally secreted by the kidneys, CrCl is used to estimate the GFR.

Creatinine Clearance as Estimate of GFR

- **Creatinine clearance rate** ($C_C$ or CrCl) = the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR (helps us to assess kidney function)

- Dosage of drugs that are excreted primarily via urine may need to be modified based on either creatinine clearance or GFR
  - Creatinine clearance/GFR is used as the standard for drug dosing

- Document CrCl/GFR in geriatric patient’s chart

- Variety of formulas to estimate the creatinine clearance/GFR

- **Modification of Diet in Renal Disease (MDRD)**
  - Only used in adults ($\geq 18$ yo)
  - Only used in chronic renal disease (NOT acute renal failure)
Factors Affecting Serum Creatinine Concentration

- Equations less accurate at GFR estimates greater than 60
  - Most labs with normal Cr simply report GFR > 60
- Muscular bulk
  - Increased creatinine generation due to increased muscle mass
- Malnutrition, muscle wasting, amputation
  - Reduced creatinine generation due to reduced muscle mass
- Vegetarian diet
  - Reduced creatinine generation
- Ingestion of cooked meats
  - Transient increase in creatinine generation
- Older age
  - Reduced creatinine generation due to age-related decline in muscle mass
- Female sex
  - Reduced creatinine generation due to reduced muscle mass
- Race (African ancestry)
  - 10% higher in African ancestry due to greater muscle mass
- Obesity
  - NO CHANGE; excess mass is fat, not muscle mass & does NOT contribute to increased creatinine generation

When should a 24 hour urine collection for creatinine clearance be performed?

- Extremes of age and body size
- Severe malnutrition or obesity
- Disease of skeletal muscle
- Paraplegia or quadriplegia
- Vegetarian diet
- Rapidly changing kidney function
- Pregnancy

- eGFR calculators do NOT replace clinical judgment!!!
Stages of Chronic Renal Failure

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<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR* mL/min/1.73m²</th>
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<tbody>
<tr>
<td>1</td>
<td>Slight kidney damage with normal or increased filtration</td>
<td>More than 90</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in kidney function</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in kidney function</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in kidney function</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>Less than 15 (or dialysis)</td>
</tr>
</tbody>
</table>

Normal Serum Creatinine

- A normal serum creatinine:
  - 0.6 to 1.1 milligrams per deciliter in women
  - 0.7 to 1.3 milligrams per deciliter in men
MDRD

- Modification of Diet in Renal Disease (MDRD)
- GFR (mL/min/1.73 m²) = 175 x (Scr)^-1.154 x (Age)^-0.203 x (0.742 if female) x (1.212 if African American) (conventional units)

Creatinine Clearance

- Creatinine clearance is estimated by the Cockcroft-Gault equation (calculated estimates of GFR)
  - Need:
    - Gender
    - Age
    - Serum creatinine
    - Weight

*This equation should only be used for patients 18 and older.

**The NKDEP presently recommends reporting estimated GFR values greater than or equal to 60 mL/min/1.73 m² simply as "≥60 mL/min/1.73 m²", not an exact number.