Following a Drug Through the Body

1. Administration – Get drug into person.
2. Absorption - Drug gets into bloodstream
3. Distribution - Blood carries drug to tissues
4. Drug Action – Drug binds to & affects cells
5. Termination of Effect, Metabolism and/or Elimination

What does “kinetic or kinetics” refer to?
1,2,3,5 = Pharmacokinetics (“drug movement”)
4= Pharmacodynamics

Routes of Administration

• Each route has advantages and disadvantages

Oral Route
(most common “enteral”or “into GI tract” route)

• Easy, convenient, accepted
• Gradual onset (5-30 min) with 75% absorbed within 1-3 hrs but may not be complete for 6-8 hrs; provides a longer lasting effect.
• Reversible for a while
• But: Not all drugs well absorbed, not all can withstand stomach acids; some upset stomach, some require large pills/capsules
• Absorption variable depending on drug, genetics, stomach contents; dosing not precise; some drug may be lost to “first-pass metabolism”

First-Pass Metabolism of Some Drugs

Liver

Some Absorption-Related Food/Drug Interactions

• Grapefruit juice increases absorption of antihistamines, codeine, tranquilizers, cardiovascular & AIDS drugs
• Pop, fruit or veggie juice or vitamins with iron can decrease absorption of erythromycin
• Dairy foods or other calcium rich items decrease absorption of tetracycline
• But food in stomach may improve absorption of other drugs (example: antipsychotic Zialet (ziprasidone))
• Excess dietary salt may decrease lithium levels; low salt levels may increase lithium levels

FYI - Don’t Take With Grapefruit

• Anti-anxiety Buspirone; benzodiazepines
• Antidepressant Sertraline (Zoloft)
• Antihistamine Fexofenadine (Allegra)
• Anti-seizure Carbamazepine (Carbatrol, Tegretol)
• Calcium channel blocker Nifedipine (Procardia),
• Statins Simvastatin (Zocor), Lovastatin (Mevacor), Atorvastatin (Lipitor)
• (this is just a partial list – check your meds)
Effect of Grapefruit on BuSpar Absorption

Something New: “Prodrugs”

- May orally administer a “prodrug” (something that will be turned into an active drug in your stomach but won’t be active otherwise)
- Example: Vyvanse for ADHD
- Lysine attached to d-amphetamine makes it inactive until the lysine is removed in stomach. The d-amphetamine won’t be active if snorted or ground up and injected.

Injection (see Table 1.1 on p 12)

- Subcutaneous (SC) or “skin-popping”
  - Slowest injection route; can irritate skin
  - Often used for insulin injections
- Intramuscular (IM)
  - Intermediate speed depending on muscle selected (arm faster than butt) & vehicle (oil or micro-encapulated injections in butt, e.g. “depot” injections of antipsychotics, or long-acting naltrexone for recovering addicts, absorbed over weeks)
  - Easier to do than intravenous

Injection Problems

- Intravenous route most dangerous because of risk of possible life-threatening reactions or allergic responses
- Risk of clots or emboli due to particles, air bubbles
- Must use sterile procedures or risk infection.
- Site of injection deteriorates with repeated injections.
- Not reversible

Inhalation

- Inhalation of gases/vapors and/or particles
- Rapid absorption in lungs & fastest route to brain (5-8 seconds)
- Fairly easy once learned
- But: Many drugs cannot be inhaled
  - Dose can be difficult to control
  - There is no drug depot or reserve
Inhalation via smoking presents special risks.
• Through Mucous Membranes (see more examples p 10)
  • Sublingual (under tongue): nitroglycerine; Suboxone
  • Buccal (held in cheek): Nicorette gum, fentanyl
  • Intranasal (sprays or snorting)
  • Narcotic 'lollipop' for kids

Sublingual
  Nitroglycerin for fast relief of angina pain
  Suboxone for recovering narcotic addicts (buprenorphine + naloxone)

Intranasal
  • Decongestant Spray
  • Imitrex Nasal Spray for Migraines
  • Decongestant Spray

Others
  • Topical – applied to skin
  • Transdermal (see p.38 examples) high tech
    continuous, controlled release of a steady dose of drug
  • Rectal – another "enteral" route (suppository or enema)
  • Implantable (Implanon birth control)

• Transdermals
  1. Nitroglycerin for Angina
  2. Contraceptive Patch
  3. Scopolamine motion sickness patch
  4. Fentanyl for pain

New 3 Day Insulin Patch
  New long-acting patches for migraine, antipsychotics and Parkinson's disease meds are being tested for commercial release
Drug Implants

New Implanon implanted Contraceptive (single progestin rod)

Implanted pump to relieve chronic pain

Other implants under development: e.g. antipsychotic implant

Routes Vary in:
- Form of drug
- Dose necessary & absorption
- Time course (start & length of effect)
- Intensity of drug effects - inhalation & intravenous most intense
- Risks & benefits

Routes Related Differences in Drug Time Course

Route - Related Differences

1. Administration - Get drug into person.
2. Absorption - Drug gets into bloodstream
3. Distribution - Blood carries drug to tissues
4. Drug Action - Drug interacts with cells
5. Termination of Effect, Metabolism and/or Elimination

- Study of 1, 2, 3, & 5: pharmacokinetics
- Study of action = pharmacodynamics

Distribution
- Bloodstream distributes drug widely (not just to the problem area)
- Drugs vary in how fast they leave blood (depends on concentration, fat-solubility of drug & whether it binds to proteins in blood)
- Presence of other drugs can alter this speed - this is one source of drug-drug interactions
- (you may skip p 42-43)

Limitations to Distribution:
- the "blood-brain barrier" excludes or slows entry of many drugs into brain. (Psychoactive drugs are the fat-soluble ones that do make it into brain.)
- the "placental barrier" excludes some large molecule chemicals but does NOT exclude psychoactive drugs.
• Following a Drug Through the Body

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What does “kinetic or kinetics” refer to?
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Why Do Drug Effects End?

• Drug may be “biotransformed” or metabolized by liver, then excreted by kidney.
• Drug may be excreted by kidney unchanged.
• Some drugs may leave in feces or other bodily fluids (milk, sweat, breath)
• Some molecules may be broken down at site of action (e.g. receptor sites in CNS) or before they are even absorbed
• Drug effect may end because the drug moves away from the site of action (e.g. from brain to body fat)

Meet the Families

Cytochrome P450 (CYP) Enzymes

• Families of enzymes found in liver & GI tract lining
• Metabolize or break down lots of chemicals
• Different subfamilies handle different drugs

CYP Families of Enzymes

• Affecting these enzymes will affect drug metabolism
  • “Grapefruit juice effect” – blocks CYPs in GI tract so LESS drug metabolized & more gets into bloodstream
  • Some drugs increase these enzymes (e.g. Tegretol) so drugs get metabolized FASTER
  • Others drugs decrease these enzymes (e.g. Prozac can decrease metabolism of Clozaril; valproate inhibits metabolism of Lamictal)
  • CYP effects are the reason behind lots of drug-drug interactions and some may be serious or even fatal
People Differ in How Much & What Forms of CYP Enzymes They Have (p.53)

- Example: A study of 1199 psychiatric patients
- These diffs may be a major reason for individual differences in drug response, side effects, & risks
- DNA test can now determine if you are a normal, slow or fast metabolizer of certain drug categories.
- “Pharmacogenetics” is a growing area of drug research.

- The rate of metabolism of most drugs varies with the concentration of drug in the body:
  - more metabolized/hr when concentration is high
  - less metabolized/hr as the concentration drops

Table 2.2: Significance of genetic testing in the determination of drug dosage for an antidepressant

<table>
<thead>
<tr>
<th>Genetic variation</th>
<th>Normal metabolizer</th>
<th>Slow metabolizer</th>
<th>Fast metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects on you</td>
<td>The antidepressant helps your depression and causes few side effects.</td>
<td>The antidepressant builds up in your body causing intolerable side effects.</td>
<td>The antidepressant is eliminated too quickly, providing little or no improvement in depression.</td>
</tr>
<tr>
<td>Treatment options</td>
<td>Follow the recommended dosage.</td>
<td>Switch antidepressants or reduce your dosage.</td>
<td>Switch antidepressants or increase your dosage.</td>
</tr>
</tbody>
</table>

Table 2.4: Half-Life calculations

<table>
<thead>
<tr>
<th>Number of half-lives</th>
<th>Amount of drug in the body</th>
<th>Percent eliminated</th>
<th>Percent remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>87.5</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>6.2</td>
<td>93.8</td>
<td>6.2</td>
</tr>
<tr>
<td>5</td>
<td>3.1</td>
<td>96.9</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>1.6</td>
<td>98.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Example: Caffeine

- Drank 8 oz. Starbucks coffee containing 250 mg caffeine at 7 PM
- Caffeine half-life "on average": ~5 hrs
- Midnite – 125 mg left in body
- 5 am 62.5 mg left in body
- 10 am 31.25 mg left in body
- 3 PM 15.6 mg left in body
- 8 PM 7.8 mg
- 1 AM 3.9 mg (98.4% has been eliminated after 6 half-lives – almost drug-free)
Sample Average Half-Lives

- Aspirin: 5-1.5 hrs
- Morphine: 1.5-2.5 hrs
- Tetracycline: 2.5-5.5 hrs
- Haldol: 6-18 hrs
- Lithium: 18-30 hrs
- Valium: ~30 hrs in young, several days in elderly

An Exception to the Rule

- Alcohol is metabolized at a steady rate, regardless of the concentration of the drug in the body.
- On AVERAGE the liver metabolizes slightly less than 1 STANDARD drink per hour, whether you have 1 drink in your body or 20.
- Elimination of drug from the body relates not only to the length of the drug effect but also the detection of the drug by a drug test.

Average Detection Time in Days

- Alcohol: up to 1
- Amphetamine: 1-4
- Benzodiazepine: 7-42
- Cocaine: 1-3; up to 12 for chronic use
- Marijuana: 1-7; up to 35 for chronic use
- Opiate: 1-3
- Phencyclidine: 2-7; up to 30 for chronic

Dose and Its Relationship to Drug Effects

(covered in Chap 3 starting p 78)

Think about your prescription & OTC medications. How is the dose usually expressed?

Pharmacokinetic Differences (Absorption, Metabolism) Cause Drug Time Course Diffs (p. 33)
Dose

- Most drugs have doses expressed in milligrams (mg.) (thousandths of a gram)
  - e.g. 200 mg tablet of ibuprofen
- Exceptions: LSD (50-150 micrograms (millionths)); fentanyl – a fraction of a milligram (.05 mg-.10 mg)

What's the Right Dose for Me?

- A rule to remember:
- Wide individual variability in drug response
- We differ in absorption, distribution, drug action, and/or metabolism/elimination.

For example, remember our question of how much you have to drink before you just start to feel the alcohol?

If you are a drinker, imagine that you go out drinking (on an empty stomach). How much or how many of the standard drinks above would you have to drink to JUST START FEELING the ALCOHOL?


What Dose Will Produce the Desired Effect in Different People?

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th># of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>70</td>
<td>15</td>
</tr>
</tbody>
</table>

ED50

Individual differences is the rule even when we have already adjusted for weight

The Dose-Response Curve

- Graphic representation relating the amount of drug administered to the response produced
- Response may be represented as intensity of response OR as % of group responding at each dose
- Curve is for a particular drug effect only
- Different effects of a drug may show different dose-response relationships.
- All drugs have multiple effects.
Another Way to Show a Dose-Response Relationship:
% Who Get Desired Response at Each Dose

Remember: curve is for a specific effect of the drug. Other effects of drug may require different dosages.

Every Drug Produces Multiple Effects

A Safer Drug:
Therapeutic vs. Toxic Effects

Measures of a Drug’s Safety

- Therapeutic Index compares the average LD to the average ED (LD50/ED50)
- LD50/ED50 (based on animal research)
  - THC  Ti=1000  Valium Ti=100
  - Morphine  Ti=70  Alcohol Ti = 10
  - Digoxin  Ti = 2  Lithium  Ti= 1.8
- More conservative “Safety Margin” LD1/ED99
  Compares the lowest LD to the highest ED likely to be used
• **Potency vs Effectiveness**

- **Potency** – related to the dose of drug required to produce a particular effect
- **Efficacy or Effectiveness** – related to the maximum possible effect obtainable from a particular drug

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A POTENCY Difference

A POTENCY Difference

A POTENCY Difference

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<table>
<thead>
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<th>Potentia vs Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency – related to the dose of drug required to produce a particular effect</td>
</tr>
<tr>
<td>Efficacy or Effectiveness – related to the maximum possible effect obtainable from a particular drug</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Sample Contents of Some Coated Tablets:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg active drug</td>
</tr>
<tr>
<td>30 mg sugars</td>
</tr>
<tr>
<td>6 mg cornstarch</td>
</tr>
<tr>
<td>9 mg miscellaneous</td>
</tr>
<tr>
<td>10 mg coating</td>
</tr>
</tbody>
</table>

With many of today’s drugs potency is not an important feature – drugs are already so potent that they have to add filler to make the pill large enough to handle.

---

<table>
<thead>
<tr>
<th>Potency Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency Differences</td>
</tr>
</tbody>
</table>

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Dose-Response Curves Showing Difference in Potency

Dose-Response Curves Showing Difference in Efficacy & Potency

---

<table>
<thead>
<tr>
<th>Potency Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency Differences</td>
</tr>
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A POTENCY Difference

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A POTENCY Difference

A POTENCY Difference

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A POTENCY Difference

A POTENCY Difference

A POTENCY Difference
Comparing Curves

- Say it with me: All drugs produce multiple effects!
- "Side-effects" are the effects not sought by the user.
- One person's desired effect may be another person's "side effect".
- Every drug has some side-effects that are quite common & others that occur more rarely.
- Side effects may be mild, disturbing or even dangerous.
- Potentially serious side-effects are often called "adverse reactions". Each year over 100,000 die from adverse reactions to properly prescribed drugs.

Side-Effects of Drugs

- Some Adverse Reactions: Hypersensitivity
  - An allergic response to a drug, usually (but not always) after the person has become sensitized to it. May cause rash, swelling, fever, or, in the worst cases, anaphylactic shock. Anaphylaxis is a life-threatening medical emergency.

- Signs of anaphylaxis:
  - Tingling lips and mouth
  - Flushing of face, body
  - Itchy eyes, nose, face
  - Hives
  - Eyes and face swelling
  - Wheezing
  - Symptoms rapidly progress to:
    - Weakness, dizziness
    - Throat swelling closed
    - Low blood pressure
    - Cardiac arrhythmia
    - Loss of consciousness
    - Possible death

Some U.S. Statistics

- 106,000 known deaths/yr due to adverse reactions to properly used drugs
- 3-4% of hospitalizations lead to adverse reactions
- 7,000 additional known deaths due to medication errors
- Don't know the # of non-fatal problems.

Some Adverse Reactions: Idiosyncratic Response

- Rare, unpredictable, highly individual response to a drug. The user may be at the extremes of the dose-response curve or may exhibit unusual physiological or behavioral responses to the drug.

http://www.youtube.com/watch?v=TTcL7u05aUU
You’ve taken this dose of this drug before, but this time you don’t experience the same degree of effect. Why?

Tolerance

- Tolerance: progressively decreasing drug effects due to regular, repeated administration.
- Some tolerance may begin to develop within a single episode of use (acute tolerance), but tolerance from regular use (protracted tolerance) is even more significant
- To experience the original degree of drug response the individual must increase their dose.

But:

- All effects of a drug may not show equal degrees of tolerance.
- And, under certain conditions, we might experience reverse tolerance or sensitization – an increased (sometimes dangerous) response after repeated use.

Mechanisms by Which Tolerance Occurs:

- Metabolic tolerance (increased liver metabolism of drug)
- Pharmacodynamic, cellular adaptive or “tissue tolerance” (cells at drug's site of action adapt to the drug)
- Behavioral or conditioned tolerance (learning/conditioning leads to decreased drug effects)

Example of Conditioned Tolerance

- Group A & Group B rats receive same dose of drug for 10 days.
- Group A always gets drug in the same setting while Group B gets the drug in a new and different setting each day.
- After 10 days Group A shows more tolerance/less drug response.
- The setting cues trigger learned counterreactions that decrease the effects of the drug.

- Rats with tolerance were more likely to survive the usual LD100:
  - Only 32% died if tested in the setting where they usually received injections
  - 64% died if tested in a situation not previously associated with drug administration
Physical Dependence:

- Body physically adapts to, & (to a certain extent) compensates for the regular presence of the drug.
- Evidence that this adaptation/compensation has occurred: User experiences withdrawal symptoms or “abstinence syndrome” if drug is not administered.
- Most withdrawal symptoms are the opposite of the drug effect.

Example: Heroin (just read lists)

<table>
<thead>
<tr>
<th>USING</th>
<th>WITHDRAWING</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Euphoria</td>
<td>• Dysphoria</td>
</tr>
<tr>
<td>• Sedation, sleep</td>
<td>• Insomnia</td>
</tr>
<tr>
<td>• Constipation</td>
<td>• Explosive diarrhea</td>
</tr>
<tr>
<td>• Analgesia</td>
<td>• Pain</td>
</tr>
<tr>
<td>• Pupil constriction</td>
<td>• Pupil dilation</td>
</tr>
<tr>
<td>• Decreased respiration, HR, BP</td>
<td>• Increased HR, BP, breathing</td>
</tr>
</tbody>
</table>

Cross-Tolerance & Cross-Dependence

- Tolerance to a drug often extends to other (usually chemically related) drugs.
- When physical dependence occurs, other chemically related drugs can “satisfy” that dependency & prevent withdrawal.

You’ve taken this dose of this drug before, but this time you don’t experience the same degree of effect. Why?

May Be Due to Drug Interactions

- Drug Interactions: Having more than 1 drug in your body can change the experienced effects.
- The presence of another drug may alter absorption, distribution, metabolism, elimination, and/or receptor interactions.

Some interaction examples:

- Additive (1+1=2) - Effects of 2 analgesics in Excedrin add together
- Synergistic (1+1=3) - Taking alcohol + another depressant can lead to more than the sum of their effects (synergism)
- Potentiating (0+1=2) - Tagamet, Zantac, birth control pills, or erythromycin can potentiate sedative effects of benzodiazepines like Xanax
- Antagonistic - Smoking can decrease the effectiveness of a wide range of medications
- Altered Side Effects - Taking alcohol and aspirin increases stomach upset

http://www.drugs.com/drug_interactions.php