• 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

• 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"

• 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 Geodon (ziprasidone))
  • Excess dietary salt may decrease lithium levels; low salt levels may increase lithium levels

• First-Pass Metabolism of Some Drugs
  • Some of drug absorbed from GI tract is immediately metabolized as it goes thru liver or through GI wall

• Effect of Grapefruit on BuSpar Absorption
  • Grapefruit juice increases absorption of BuSpar, certain antibiotics, certain blood thinners, certain heart medicines, certain antacids
  • Grapefruit juice decreases absorption of BuSpar, certain heart medicines, certain blood thinners, certain antacids
  • Grapefruit juice may increase or decrease levels of BuSpar, depending on the interaction
  • Grapefruit juice may increase or decrease levels of other drugs, depending on the interaction

• Routes of Administration
  • Each route has advantages and disadvantages
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-encapsulated 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 injections deteriorates with repeated injections.
- Not reversible

Injection or Infusion

- Intravenous (IV)
  - Fast (~ 15 seconds to brain)
  - Bypasses absorption obstacles
  - Most difficult & risky route
  - All injection routes give good control of dose
  - Implantable medication port for IV access

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 injections deteriorates with repeated injections.
- Not reversible

Table 1.1 Some characteristics of drug administration by injection

<table>
<thead>
<tr>
<th>Route</th>
<th>Absorption pattern</th>
<th>Special efficacy</th>
<th>Limitations and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Centralized</td>
<td>Remotely lethal</td>
<td>Requires specialized equipment or needles</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Prompt action from intramuscular</td>
<td>May cause pain and bruising</td>
<td>Requires skillful technique</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Prompt action from subcutaneous site</td>
<td>May cause pain and bruising</td>
<td>Requires skillful technique</td>
</tr>
</tbody>
</table>
• Through Mucous Membranes
  (see more examples p. 10)
  • Sublingual (under tongue): nitroglycerine; Suboxone
  • Buccal (held in cheek): Nicorette gum
  • 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
  Immitrex Nasal Spray for Migranes
  • Imitrex Nasal Spray for Migranes

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

Other Transdermals
  • Nitroglycerin for Angina
  • Contraceptive Patch
  • Scopolamine motion sickness patch
  • Fentanyl for pain

New Developments
  • Patches consisting of tiny (pain-free) microneedles to replace things like insulin injections
  • Low frequency ultrasound waves or elec. current can also increase absorption
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)
- Implant 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

Route-Related Differences in Drug Time Course

- 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

- 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.
Pharmacokinetic Differences Cause Time Course Diffs

- **Why 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).

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.
- 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); others decrease or the action of these enzymes (e.g., Prozac can decrease metabolism of Clozaril; valproate inhibits metabolism of Lamictal).
  - Reason behind lots of drug-drug interactions and some may be serious or even fatal.

Don’t Take With Grapefruit (also at least 79 other drugs)

- 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)

Rate of Metabolism

- Your genetic makeup influences how quickly you metabolize different drugs. DNA tests can now determine if you are a normal, slow or fast metabolizer of certain drug categories.
- 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.
The “Half-Life” of a Drug:

- The time it takes for half the available drug to be eliminated from the body, as measured by a 50% drop in blood levels.
- With each successive half-life another 50% of the remaining drug in the blood will be eliminated.
- Knowing half-life is important for understanding time course of drug and how often to administer it.
- A drug’s effects may be longer and more intense if liver and/or kidney are not functioning up to par.

Example: Caffeine

- Drank 8 oz. Starbucks coffee containing 250 mg caffeine at 7 PM
- Caffeine half-life “on average”: 3.5–5 hrs (I am using 5 hr in this example)
- Midnite – 125 mg left in your 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% has been eliminated in 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 in 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