•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

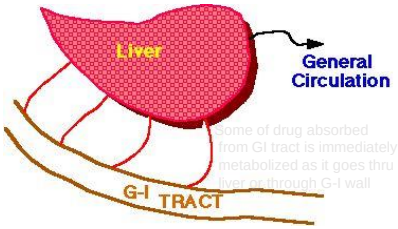
- Each route has advantages and disadvantages

•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"

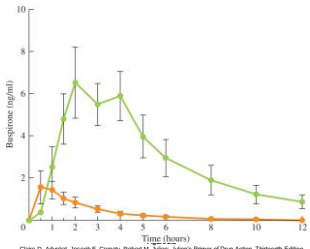
First-Pass Metabolism of Some Drugs



•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

Effect of Grapefruit on BuSpar Absorption



Claire D. Advokat, Joseph E. Comaty, Robert M. Julien: Julien's Primer of Drug Action, Thirteenth Edition
Copyright © 2014 by Worth Publishers

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.

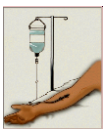
•In

- 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.

Injection (see Table 1.1 on p 12)

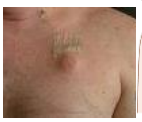
- Subcutaneous (SC) or "skin-popping"
  - Slowest injection route; can irritate skin
  - Often used for insulin injections
- Intramuscular (IM)
  - Intermediate speed depending on muscle selected (arm faster than butt) & vehicle (oil or micro-encapulated injections in butt, e.g. "depot" injections of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

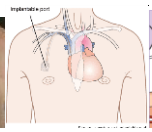
V Injection or Infusion

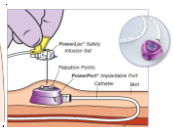


- Intravenous (IV)
  - Fast (~ 15 seconds to brain)
  - Bypasses absorption obstacles
  - Most difficult & risky route
- All injection routes give good control of dose

Implanted 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 2.1 Some characteristics of drug administration by injection

Route	Absorption pattern	Special utility	Limitations and precautions
Intravenous	Absorption circumvented Potentially immediate effects	Valuable for emergency use Permits titration of dosage Can administer large volumes and irritating substances when diluted	Increased risk of adverse effects Must inject solutions slowly as a rule Not suitable for oily solutions or insoluble substances
Intramuscular	Prompt action from aqueous solution Slow and sustained action from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant medication May interfere with interpretation of certain diagnostic tests (e.g., creatine phosphokinase)
Subcutaneous	Prompt action from aqueous solution Slow and sustained action from repository preparations	Suitable for some insoluble suspensions and for implantation of solid pellets	Not suitable for large volumes Possible pain or necrosis from irritating substance

Table 2.1
Claire D. Advokat, Joseph E. Comaty, Robert M. Julien: Julien's Primer of Drug Action, Thirteenth Edition
Copyright © 2014 by Worth Publishers

•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

Imitrex Nasal Spray for Migraines

• Decongestant Spray

http://news.yale.edu/2013/12/02/single-spray-oxytocin-improves-brain-function-children-autism

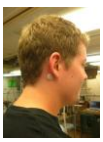
Others

- 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



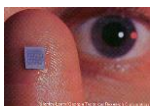
Scopolamine motion sickness patch

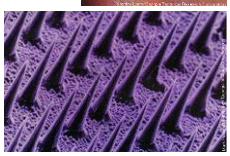
Fentanyl for pain

for depression

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)

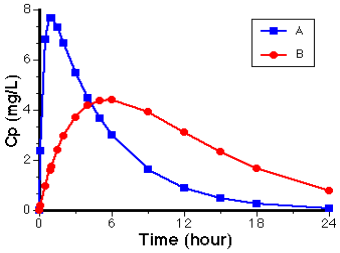
Implanted pump to relieve chromic pain

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



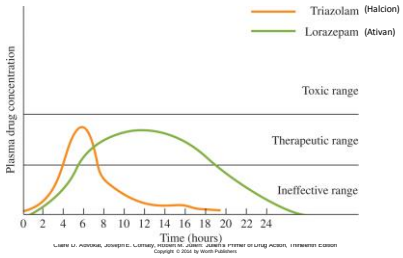
●Distribution

- 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

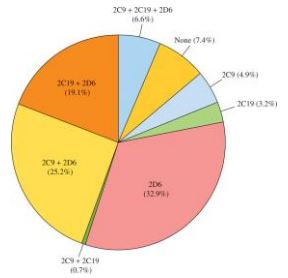


Figure 2.13
Claire D. Advokat, Joseph E. Comaty, Robert M. Julien: Julien's Primer of Drug Action, Thirteenth Edition
Copyright © 2014 by Worth Publishers

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

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

	Normal metabolizer	Slow metabolizer	Fast metabolizer
Genetic variation	Your genes produce a typical amount of enzyme.	Your genes produce too little enzyme.	Your genes produce too much enzyme.
Effects on you	The antidepressant helps your depression and causes few side effects.	The antidepressant builds up in your body, causing intolerable side effects.	The antidepressant is eliminated too quickly, providing little or no improvement in depression.
Treatment options	Follow the recommended dosage.	Switch antidepressants or reduce your dosage.	Switch antidepressants or increase your dosage.

Table 2.2
Claire D. Advokat, Joseph E. Comaty, Robert M. Julien: Julien's Primer of Drug Action, Thirteenth Edition

•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'm 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-lifes – 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