Pharmacology 101

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Objectives

- Define Pharmacology, Pharmacokinetics and Pharmacodynamics
- Understand how drug interactions work
- Understand how some specific drugs behave in the body (opioids, benzodiazepines, amiodarone)
- Apply pharmacology principles into practice

Medication Errors and Adverse Drug Events

- Error: An error of commission or omission at any step along the pathway that begins when a clinician prescribes a medication and ends when the patient actually received the medication.
- ADE: Harm experienced by a patient as a result of exposure to a medication. ADE does not necessarily indicate an error or poor care. However, ~1/2 of ADEs are preventable.

Anyone here ever seen a medication error or adverse drug event?

Anyone here ever made a medication error?

How many different prescription medications are available on the
U.S. market?

1,000

So, it’s no surprise why we see so many problems……

EXCEPT…….

The real number is 10,000

Adverse Drug Events

- ~1/3 of U.S. adults use 5 or more medications
- Annually, ADE = 700,000 ER visits and 100,000 hospitalizations
- So, is pharmacology important to your work?
- Additionally, 5% of hospitalized patient experience an ADE during their stay
- High risk: Anticoagulants, Opioids, Insulin, Cardiac, and Transitions of Care

Adverse Drug Events, cont.

- Elderly are more susceptible
- Pediatrics patients more susceptible (weight-based dosing), especially liquids
- Caregivers and patients admittedly commit medication administration errors at high rates
- 50% of ER visits for ADEs in Medicare patients are related to 4 drug classes:
  - Antidiabetic agents, oral anticoagulants, antiplatelet agents and opioid pain medication

ADE and Pharmacology

- The understanding pharmacology elucidates the pathology behind every adverse drug event
  - Therapeutic Window
  - Toxicity
  - Side Effect Profile
  - Immunologic Drug Reactions
  - Drug-Drug Interactions
  - Drug-Disease Interactions

Pharmacology

- The science or study of drugs: Their preparation, properties, uses and effects
  - Pharmacologic vs. Toxicologic
  - Early pharmacologists focused on plant extracts
  - Now, many synthetic compounds rule the markets

Desirable Drug Properties

- Rapid Sequence Intubation
  - Rapid Onset, Rapid Offset
  - Wide Therapeutic Window
  - No Effect on Hemodynamics
  - Blunt Sympathetic Response
  - Analgesic Properties
  - Not a Controlled Substance
  - Cheap (Avoid wallet toxicity)
- No Drugs are Perfect

Pharmacokinetics

- The study of the effect the body has on drugs
  - How does the drug get into the body?
  - Where does it go?
  - What does the body do to the drug?
  - How does the body get rid of the drug?
- The process by which a drug is absorbed, distributed, metabolized and eliminated by the body

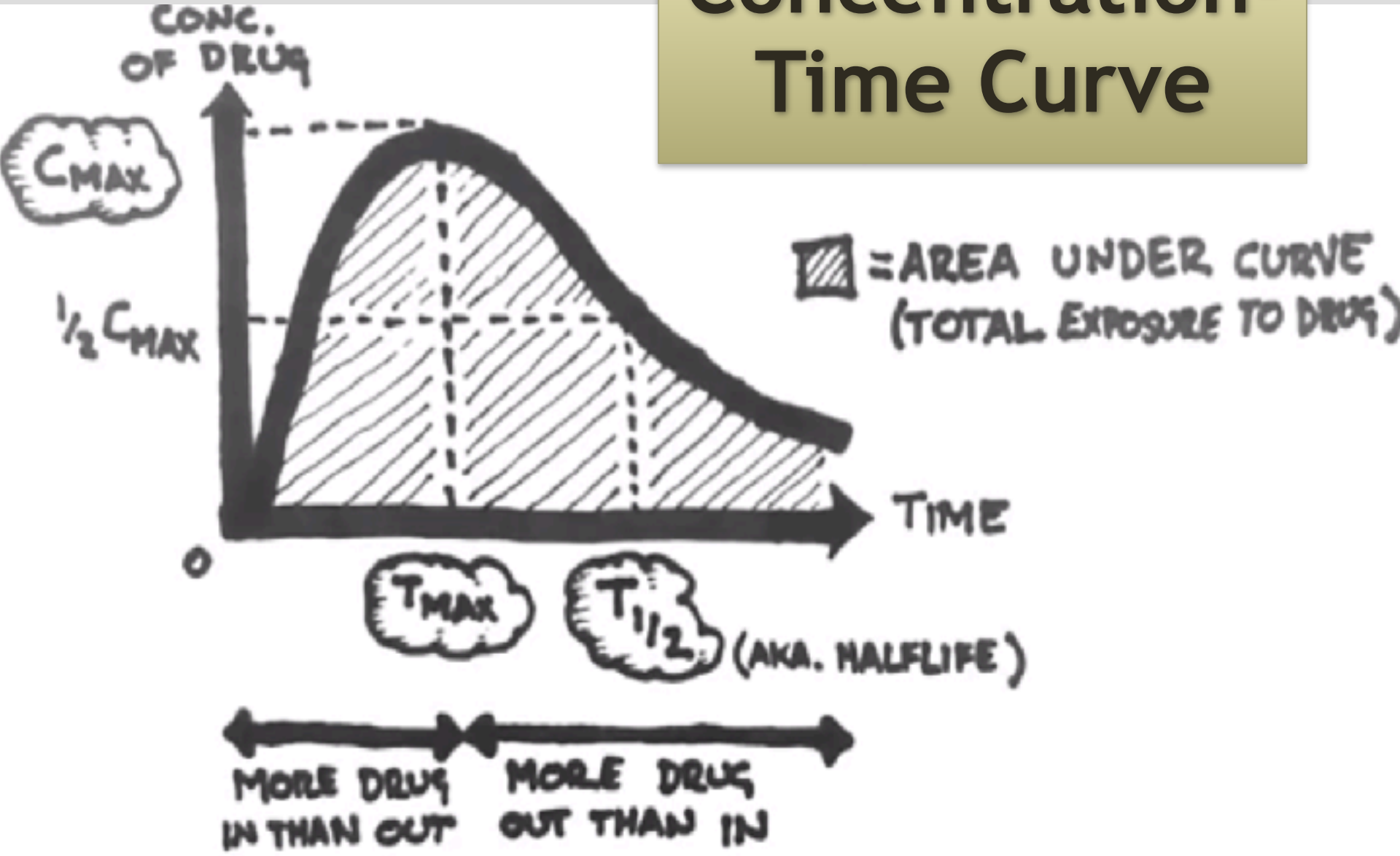
Pharmacokinetics

- ADME
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Body Water

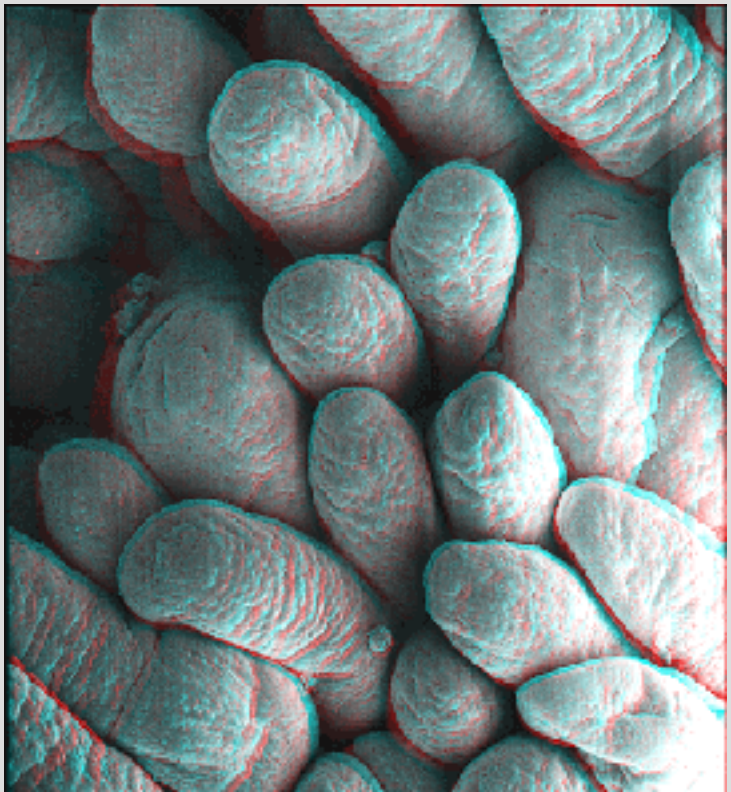
- What % of your body is water?
- How many different “compartments” make up this volume?
- Drugs distribute and establish equilibrium through these different compartments

Concentration-Time Curve



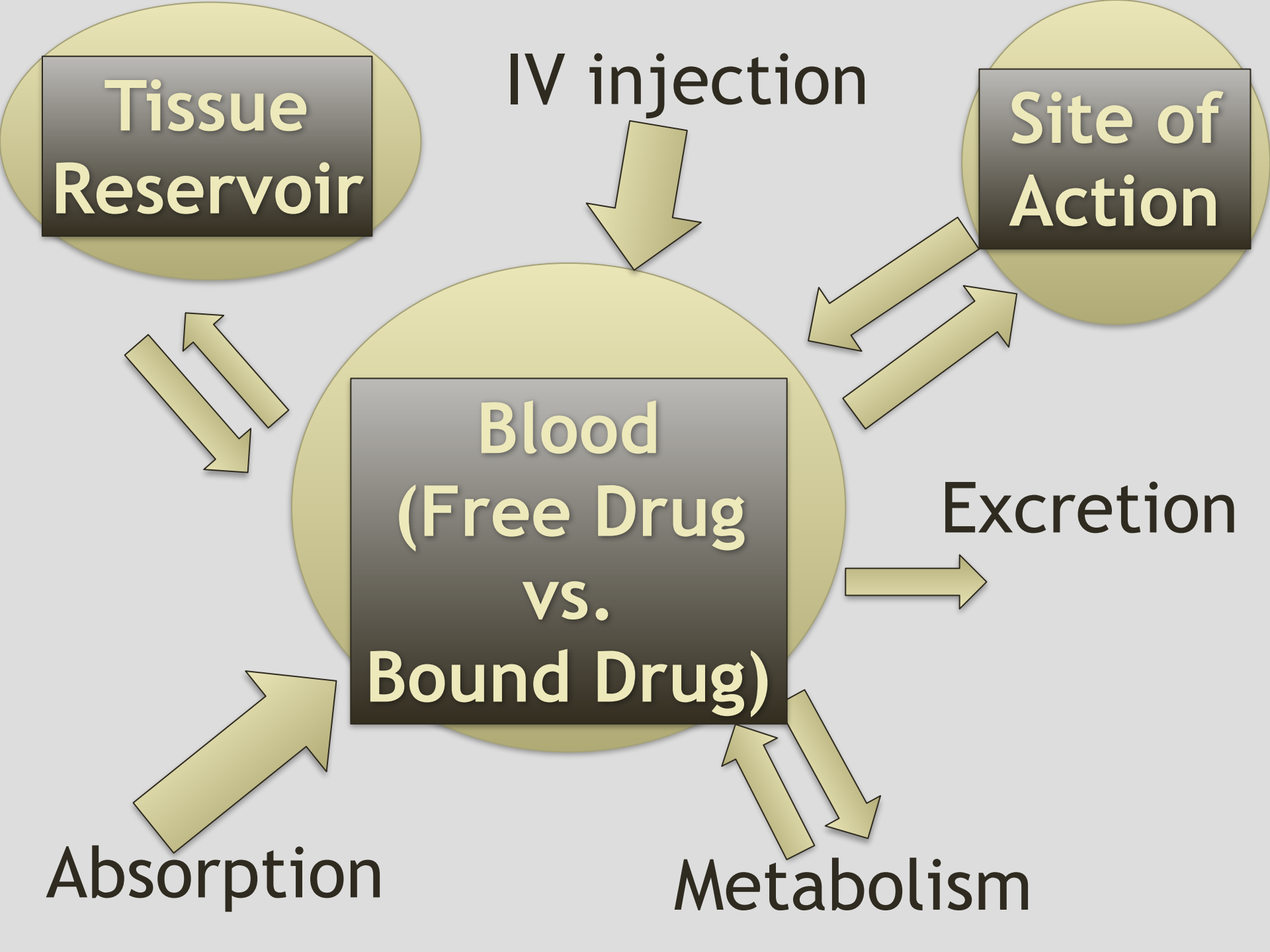
Bioavailability and Absorption

- Bioavailability (F)
  - The percentage of administered dose that reaches the bloodstream
- Gastrointestinal tract
  - Formulation
  - Food
  - Gut bacteria
  - Motility
  - Drug Interactions



Distribution

- Drugs distribute into different tissues throughout body
- Fluid Compartments
  - Blood, Extracellular, Intracellular, Fat, CSF, Cardiac
- Equilibrium
  - With time and repeat dosing at appropriate time intervals achieve an equilibrium or “steady state” when the drug into the body = drug out of the body

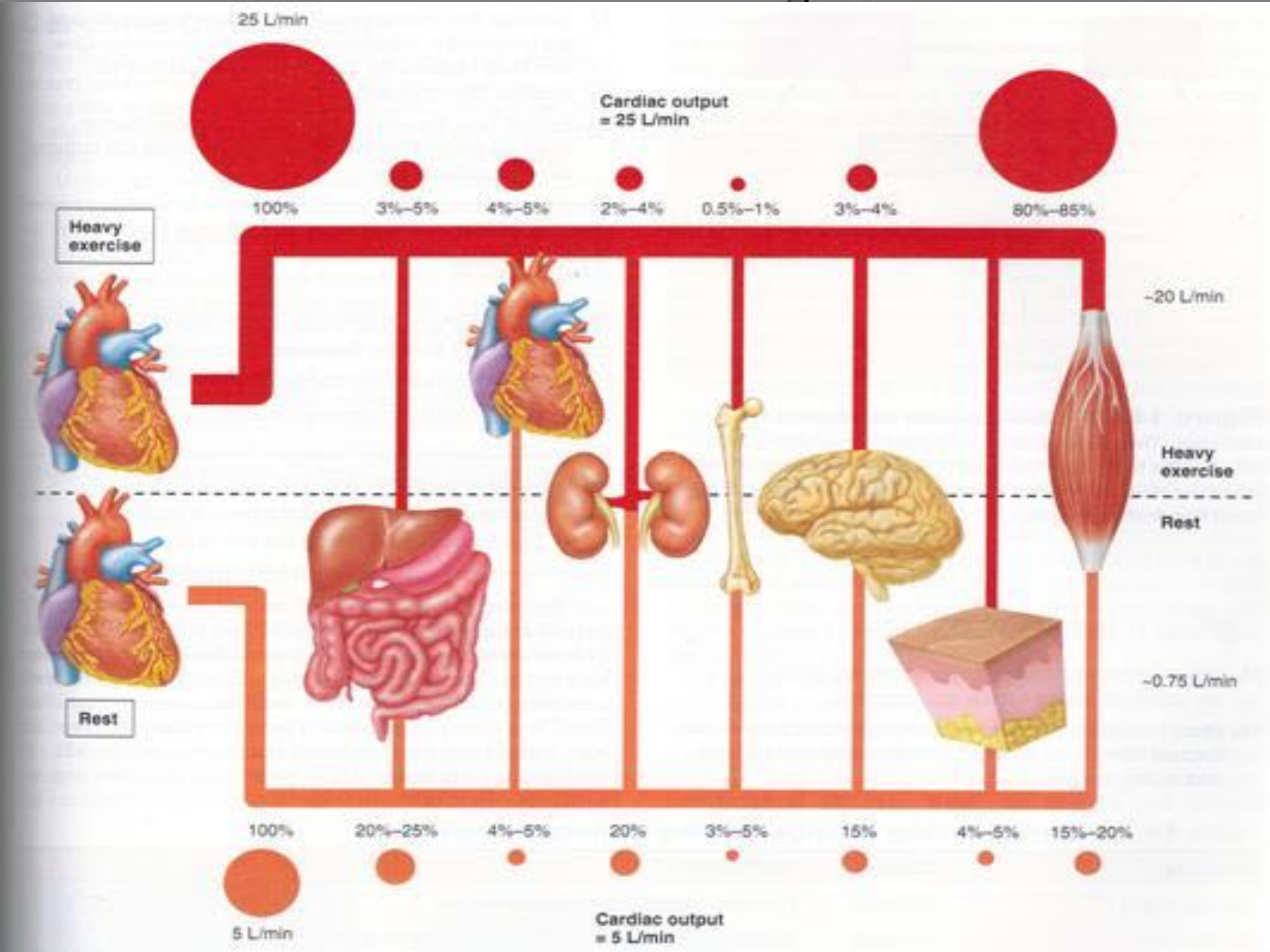

Tissue Reservoir
IV injection
Site of Action
Blood (Free Drug vs. Bound Drug)
Excretion
Absorption
Metabolism

Volume of Distribution V_D

- Definition: The size of a compartment necessary to account for the total amount of drug in the body if it were present throughout the body at the same concentration found in the blood
- $V_D = \frac{\text{Total amount of drug in the body}}{\text{Measured Concentration in the Blood}}$
- High, the drug penetrates extensively into body tissues and leaves the bloodstream
- Low, the drug mostly remains in the bloodstream

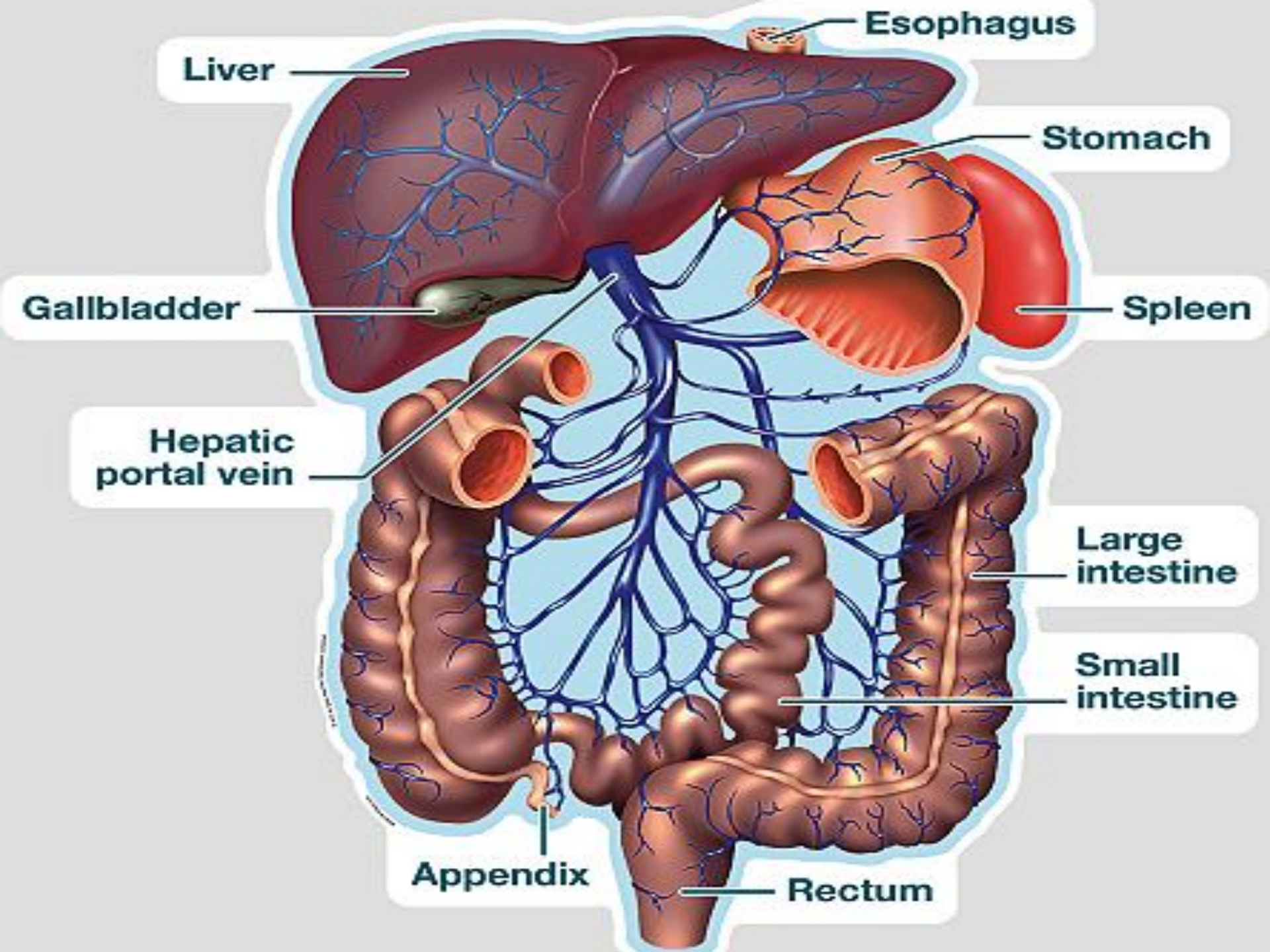
Factors Affecting Distribution

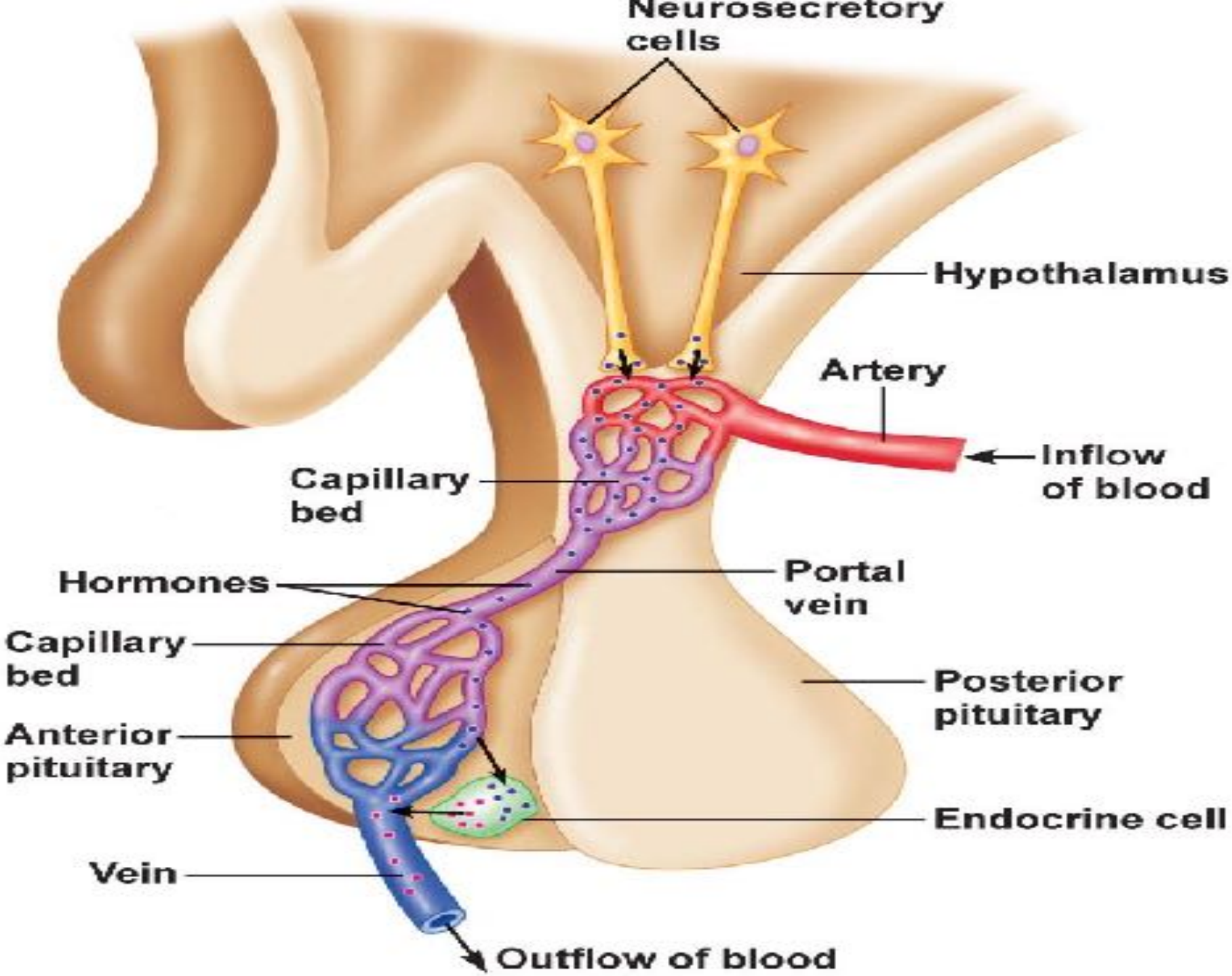
- Blood Flow
- Water Solubility (hydrophilicity) vs. Fat Soluble (lipophilicity)
- Size of Drug (large proteins stay in bloodstream)
- Permeability of Membranes
- pH of tissue


25 L/min
Cardiac output
= 25 L/min
100%
3%–5%
4%–5%
2%–4%
0.5%–1%
3%–4%
80%–85%
Heavy exercise
~20 L/min
Heavy exercise
Rest
Rest
~0.75 L/min
100%
20%–25%
4%–5%
20%
3%–5%
15%
4%–5%
15%–20%
5 L/min
Cardiac output
= 5 L/min

Metabolism

- Biochemical transformation of one substance into another
  - Pro-drug → Active drug, active metabolite, inactive metabolite
  - In general, more hydrophilic (water soluble)
- Liver (Primary)
  - Hepatic Portal System
  - First-Pass Metabolism
- Lung
- Kidney


Esophagus
Liver
Stomach
Gallbladder
Spleen
Hepatic
portal vein
Large
intestine
Small
intestine
Appendix
Rectum


Neurosecretory cells
Hypothalamus
Artery
Inflow of blood
Capillary bed
Hormones
Portal vein
Capillary bed
Posterior pituitary
Anterior pituitary
Endocrine cell
Vein
Outflow of blood

Metabolism cont.

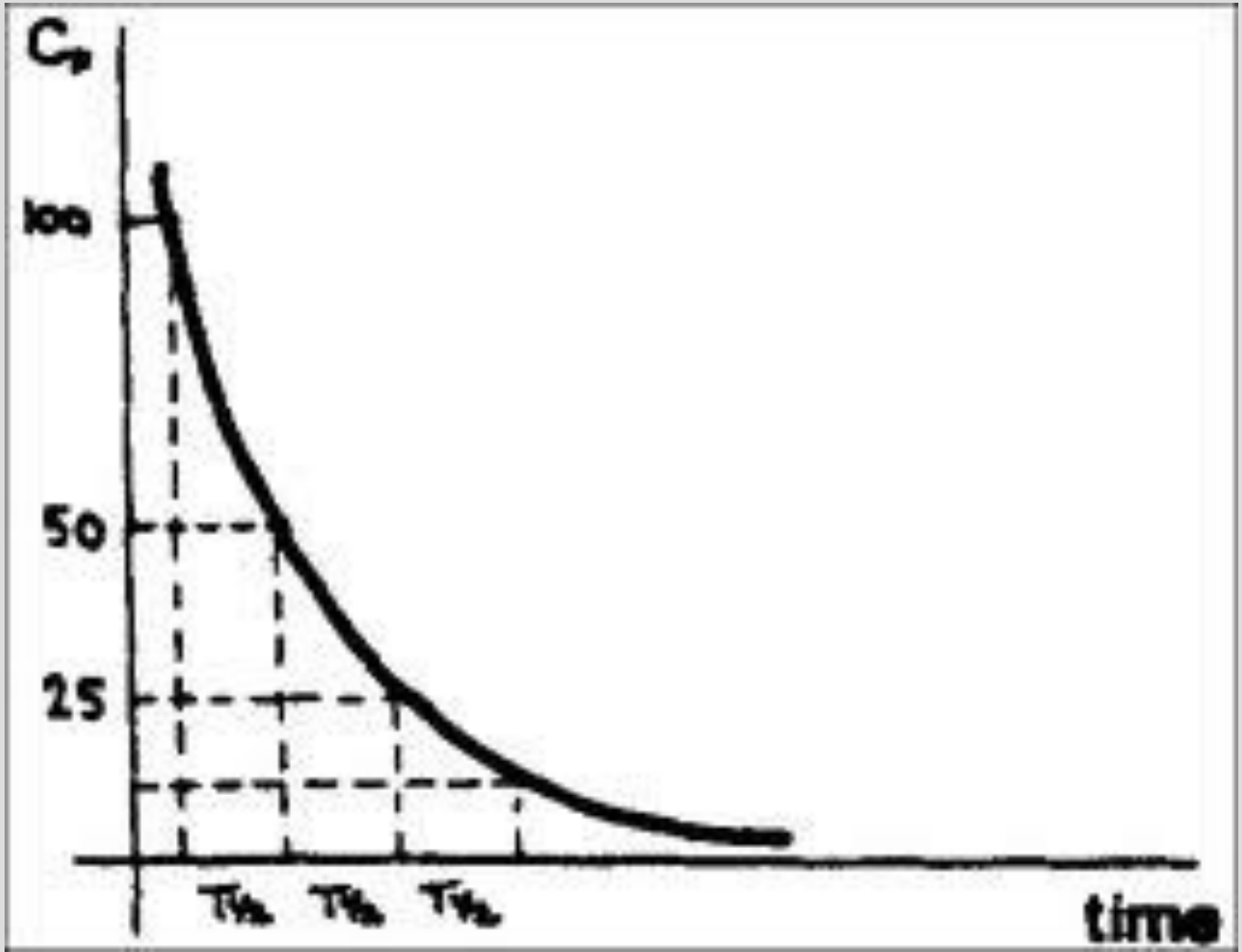
- CypP450 enzyme system (~75%)
- Found in cells and usually impact small molecules
- Induction vs. Inhibition
  - Induction: Increase number/activity of enzymes
    - Chronic alcoholism before cirrhosis
  - Inhibition: A drug “blocks” an enzyme from metabolizing other drugs
    - Acute alcohol ingestion

Excretion

- Process by which a drug is eliminated from the body
  - Metabolite
  - Active Drug
- Primarily in urine via the kidneys
- Other sites include liver → poop, sweat glands, lungs, mammary glands

Half Life ($t_{1/2}$)

- Time it takes for the concentration of a drug to drop to half of it's current concentration



First-Order Kinetics

- More drug, the quicker it is removed from the body
- A constant % is removed per unit time
- In toxic situations, the body's ability to remove drug may become saturated and the concentration of drug can rise sharply as a result and move to zero order elimination

Zero Order Kinetics

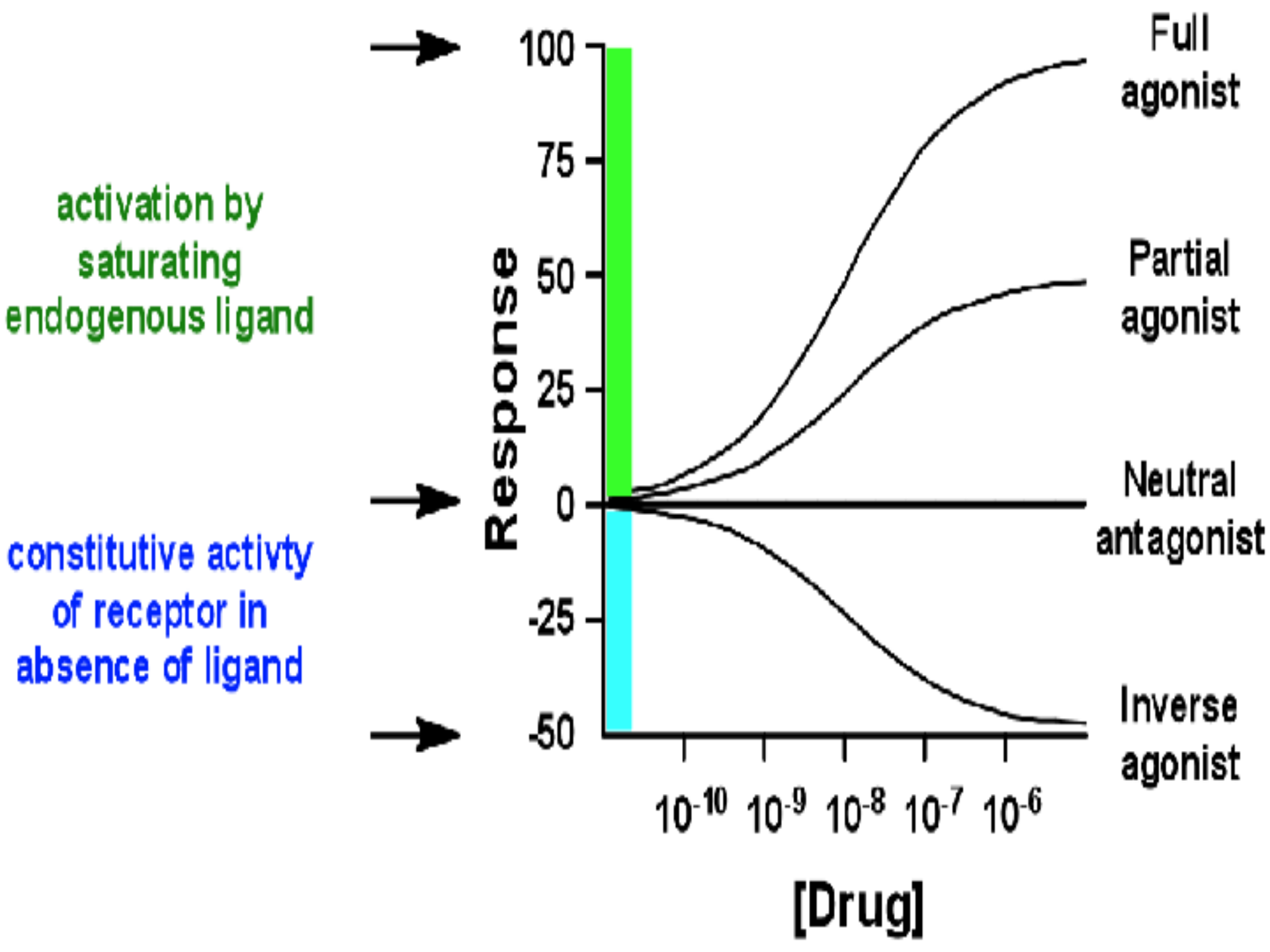
- Drug is removed at a constant rate from the body regardless of the amount in the body
- A certain amount is removed per unit time
- Example: ethanol exhibits zero order kinetics
  - 1 drink is removed from the body per hour

Pharmacodynamics

- The study of the effect a drug has on the body
- What does the drug do to the body?
- The interactions of a drug and the receptors responsible for its action in the body
- What receptors does it act on?
- What is the clinical effect?
- What are the side effects?

Pharmacodynamics

- Site of action
- Receptor-ligand relationship
  - Agonist vs. antagonist vs. partial agonist
- Selectivity/Affinity
- Physiologic response
  - HR, BP, CNS stimulation, CNS depression, vasodilation, vasoconstriction, antiplatelet, anticoagulant, antihistamine, anti-inflammatory etc.


activation by saturating endogenous ligand
constitutive activty of receptor in absence of ligand
Response
100
75
50
25
0
-25
-50
Full agonist
Partial agonist
Neutral antagonist
Inverse agonist
10-10 10-9 10-8 10-7 10-6
[Drug]

Partial Agonist

- Bind to and activate receptor, but with only partial efficacy compared to a full agonist
- Buprenorphine (Suboxone)
  - Strong binding to opiate receptors with only partial activation
    - Pain management complications
  - Mixed with naloxone (why?)
  - Reversible with naloxone?

Drug Interactions

- Pharmacokinetic
  - Absorption
  - Distribution (protein binding)
  - CypP450 enzyme system
- Pharmacodynamic
  - Competition for active site
    - Opioids and Narcan
  - Additive or Synergistic effects on same system
    - Opioids and benzodiazepines on respiratory center
    - Synergy: when 1 + 1 = 3
    - Nitrates and Viagra

Drug Interactions (Kinetic vs. Dynamic)

- Warfarin and many, many other drugs affecting the CypP450 enzymes, especially, antibiotics and some antidepressants
- Antiplatelets and anticoagulants
- Antidiabetic agents, especially those actively lowering blood glucose
- Cardiac Agents, esp. BP lowering or drugs which may increase potassium (spironolactone, ACE inhibitors)
- Be very suspicious especially when recent additions to a medication list

Morphine

- Named after Morpheus, the Greek God of Dreams
- Many synthetic opioids now produced
  - Hydromorphone
  - Fentanyl
  - Methadone
  - Hydrocodone
  - Oxycodone

Potency

- What is more potent?
  - Morphine 5 mg IV or 15 mg PO?
  - Heroin in the 60's or heroin today?
  - Fentanyl 50 mcg IV or Dilaudid 1 mg IV?

Potency

- A measure of drug activity expressed by the amount required to produce an effect of given intensity
- Morphine is morphine
- Heroin today often is of better quality (higher than 90% pure diacetylmorphine)
- Fentanyl is more potent than hydromorphone

Morphine Pharmacodynamics

- Binds to opioid receptors (mu-μ, kappa-κ, delta-δ)
- Agonist
- What are these receptors for?
- Endorphins, enkephalins, endomorphins
  - Found in brain, GI tract, peripheral sensory neurons
- Mechanism of action
  - Inhibits ascending pain pathways altering the perception of and response to pain
- Tolerance develops

Morphine Pharmacokinetics

- Bioavailability (PO)
  - 17-33% (15 mg PO = 5 mg IV)
- Distribution
  - 3-4 L/kg
- Metabolism
  - Hepatic (liver) via glucoronidation to morphine-6-glucoronide (active, neurotoxic metabolite) and morphine-3 glucoronide (inactive metabolite)
- Excretion
  - 90% urine (as metabolites) 10% feces

Benzodiazepines

- Drug of choice for emergent treatment of Status Epilepticus
- Highly lipophilic (fat soluble)
  - Readily crosses blood-brain barrier
- MOA: Bind to and activate GABA receptors
- What % of blood goes to brain?
- 2 compartment model
  - First to vessel-rich, highly perfused tissues
  - Next, redistribution to muscle and fat
- Reversible with?

Amiodarone

- High Volume of Distribution (66L/kg)
- Long Half-Life 40-55 days
- Bioavailability is only 20-55%
- Class III antiarrhythmic
  - Alpha, Beta and Ca^{++} Channel blocking properties
- Excreted in bile by liver, lacrimal glands and skin, not by kidney, so no renal adjustment
- Initial dosing is ~ 1000 mg IV day 1 then 720 mg/day IV
- Maintenance dose ~200 mg PO daily

Where can I get quality drug information?

- For basic information for patients or just to rough up on what a drug is for and common adverse reactions/side effects, visit www.iodine.com
- Washington State University Drug information Center
- Poison Control 1-800-222-1222
- Lexi-Comp (hard copy)

Case 1

- MIA is 50 y.o. 400 lb ex-blockbuster employee with a skinny face
- Life-long 2 PPD smoker, recently switched to vaping because it was “cooler”
- Drinks 5-6 Mike’s Hard Lemonades each morning
- Lives in Malaga with wife, 12 cats, and pet Gerbil “Gandalf”
- PMH: CAD, COPD, DM, Afib
- Recently discharged (3 days ago) from CWH after a COPD exacerbation
- EMS called because patient was disoriented and lightheaded after having BRBPR
- EMS arrives at home to transport patient back to ER
- EMS collects history on patient with wife present including medication history
- The ask the following questions:

Questions for Patient and Wife

- What medications does the patient take?
- When was the last dose of each medication?
- Were there any medication changes or new medications the patient was taking after the hospitalization?
- Do they have a list of the medications the patient was supposed to be taking after discharge?

Medication List

- Lisinopril 5 mg daily
- Warfarin 5 mg as directed by anticoagulation clinic
- Levofloxacin 500 mg daily for 5 days
- Carvedilol 12.5 mg daily
- Prednisone 40 mg daily with taper
- ASA 81 mg daily
- Metformin 1000 mg BID
- Lantus 25 units HS
- Glipizide 5 mg BID
- Tussionex 1 tbsp PRN cough
- Metoprolol XL 50 mg daily

More Questions

- Which medications were new post-hospitalization?
- Which Rx bottles were old vs. new?
- When was last INR?
- When was last blood sugar check?
- Diet in past 24 hours?
- Can I see medication bottles patient has been using?

Report to ED Physician

- MIA found hypotensive with BG of 50 and BRBPR.
- Patient recently discharged on abx and warfarin with last INR check during hospitalization
- Patient with new Rx for Lantus, was supposed to stop glipizide post-discharge but continued taking both
- Also, patient was apparently changed from carvedilol to metoprol XL during last admission but patient was also taking both these medications
- Here is the AVS from the last hospitalization for your information

Conclusion

- Pharmacokinetics- What the body does to the drug
- Pharmacodynamics- What the drug does to the body
- Drug Interactions can be pharmacokinetic or pharmacodynamic in nature
- Understanding drug pharmacology is important to the paramedic and can help them do their job well and convey important information to receiving facilities

Thank You!