USMLE Step 1: Review of Pharmacodynamics & Pharmacokinetics

Dennis R. Koop, PhD.
koopd@ohsu.edu; 4-7803

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Drugs are Big Part of Step1!!
What Do You Need to Know?

- What is the problem?
- Is a drug needed?
- Which class of drugs would you choose?
- Which would work and why?
- How do they work?
- Is there a drug interaction with current drug therapy?
- How much would you give and for how long?

Key Concepts to Learn

- PD
  - Receptor Binding
  - Signaling
  - Receptor Selectivity
  - Agonist v. antagonist
- PK
  - Bioavailability
  - Volume of Distribution
  - Clearance
  - Elimination $T_{1/2}$
  - Accumulation
  - Steady-state reached in $4 \times$ Elimination $T_{1/2}$
- PD & PK Drug, Disease & Age Interactions
Selectivity versus Specificity

- If a drug has one effect, and only one effect on all biological systems it is **Specific**
- Vast majority of drugs are **Selective**
  - Will exhibit activity at more than one receptor site if concentration is high enough
  - Propranolol is a non-selective $\beta$-adrenergic antagonist where as albuterol is a selective $\beta_2$– agonist.
  - Verapamil is a L- type calcium channel blocker but will also block sodium channels at high concentrations.

Suffix list for biologics and peptides

- **mab** = monoclonal antibody
- **ximab** = chimeric(mouse-human) monoclonal antibody
- **zumab** = Humanized monoclonal antibody-ie. reducing the amount of mouse to under10%
- **umab** = Human monoclonal antibody
- **cept** = receptor–antibody fusion protein that mimics an immunoglobulin
- **tide** = peptides synthetic or recombinant
Suffix list in addition to those in First Aid 2013

- **stadin** = HMG-CoA reductase inhibitors (atorvastatin)
- **tinib** = kinase inhibitors (imatinib; ruxolitinib)
- **prazole** = proton pump inhibitors (omeprazole)
- **semide** = loop diuretics (furosemide)
- **xaban** = direct factor Xa inhibitors (rivaroxaban)

Pharmacodynamics (PD)

- Study of time to onset, magnitude, duration and mechanisms of drug effects.
- **What the drug does to the body!**
- Determines what drug class and how much of that drug you prescribe.
- Determines the therapeutic and toxic C_p ranges.
Agonist

• Agent which activates a receptor and its associated effector system to produce a response.

• Partial agonist is an agonist that has less efficacy than a full agonist (must compare).

Graded Log-Dose Response

• **Efficacy** - The maximal effect produced by a drug is termed the maximal efficacy. Potency has nothing to do with efficacy and of the two the efficacy is more important. Drug A is more efficacious than B.
Graded Log-Dose Response

- **Potency** - The location of the curve along the dose axis or the amount of drug needed to cause some effect. Not important clinically as long as the dose can be safely delivered. These are usually compared by ED50. Drug A is more potent than C.

Rank Order Potency for Opioids

- Morphine: IV dose 10 mg
- Hydromorphone: IV dose 1.5 mg
- Fentanyl: IV dose 0.05 mg
- Codeine: Oral dose 200 mg (prodrug)
Antagonist

- Agent which binds to a receptor but does not produce a response. An antagonist can block the actions of an agonist.
- There may be only a modest change in drug structure to convert an agonist into an antagonist.

Structure-Activity

![Morphine (agonist)](image1)
![Naloxone (antagonist)](image2)
![Naltrexone (antagonist)](image3)
![Methylnaltrexone (antagonist)](image4)
Effect of agonist

Log-Dose

Log-Concentration

50%

$B_{\text{max}}$

$K_d$

Competitive Antagonist

• An antagonist that can be overcome by increasing concentrations of agonist.
• Dose response curves are shifted to the right (an apparent decrease in affinity of the agonist for the receptor)
• Most antagonists in clinical use are competitive antagonists
You have a patient who is exhibiting signs and symptoms of an opioid overdose. You pull a vial of methylmethatrexone and inject it intravenously. Despite this effort the respiratory rate continues to decline. Why was the antagonist not effective??
Structure-Activity

Morphine (agonist)  Naloxone (antagonist)  Naltrexone (antagonist)

Methylnaltrexone (antagonist)

Noncompetitive Antagonism

• An antagonist where the inhibition cannot be overcome by increasing concentrations of the agonist.
• This is often also termed irreversible antagonism but it need not be a covalent modification of the receptor.
Noncompetitive Antagonists

Effect

$E_{\text{max}}$

Log-Concentration of Agonist

Effect of Aspirin on COX 1/2

Aspirin

Prostaglandin Production

Log-[Arachidonic acid]
Although it does not act at any histamine receptor, epinephrine reverses many effects of histamine. Epinephrine is a:

A) Chemical antagonist of histamine  
B) Competitive inhibitor of histamine  
C) Metabolic inhibitor of histamine  
D) Noncompetitive antagonist of histamine  
E) Physiologic antagonist of histamine

Quantal Log-Dose Response

- Plot the data from a frequency distribution curve as a cumulative frequency
- Similar plots would be obtained for all the effects of a drug; may not be the same
- Slope indicator of variability of the population
Therapeutic Index

• Take the ratio of:
  – $TD_{50} / ED_{50}$
• The slope of the two curves need not be parallel

LD$_{50}$ = TD$_{50}$

Therapeutic Index for NSAIDs

Log ibuprofen or celecoxib
Pharmacokinetics (PK)

- Study of rates and mechanisms of drug administration, absorption, distribution, biotransformation and excretion.
- **What the body does to the drug!**
- Determines how much of, and how often, you administer the drug.
- Determines when the therapeutic $C_p$ is reached and when $C_p$ should be measured.

PK-ADME

**PK:** Pharmacokinetics; relationship between dose and drug concentration at the site of action, and the time course of drug concentration in the body.

**A:** Absorption; the process by which administered drug achieves systemic exposure and therapeutic concentrations at the site of action.

**D:** Distribution; the process by which drug in circulation is taken up by organs and tissues.

**M:** Metabolism; the process by which drug molecules are converted to different chemical entities, usually by enzymes in the body.

**E:** Elimination; the processes by which drug is removed from the body.
Routes of Administration

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<td>First pass liver metabolism</td>
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<td>Plasma protein binding in blood</td>
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<td>Elimination through liver and/or kidneys</td>
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<td>Permeation of capillary epithelial barriers into target tissue/organ</td>
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<td>☑</td>
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<td>Plasma membrane permeation of target cell</td>
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Distribution of Drug in Body
BioDelivery Sciences International, Inc. received approval (June 9, 2014) for Bunavail (buprenorphine and naloxone) buccal film (CIII) from the FDA. The drug combination is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support. The film allows for the efficient and convenient delivery of buprenorphine while potentially overcoming some of the administration challenges presented by the sublingual dosage forms such as Suboxone. The film provides twice the bioavailability of buprenorphine compared to other formulations.

1. What would be the relative dose needed of buprenorphine as Bunavail compared to Suboxone?

2. Why would the bioavailability be greater for Bunavail?

3. If the antagonist, naloxone, is also present, why is this opioid effective?

![buprenorphine and naloxone](image)

### Organs for Drug Clearance

Liver & Kidney are the Most Important Sites of Drug Clearance

**Total Body Clearance** ($Cl_T$) = $Cl_H$ + $Cl_R$ + $Cl_{other}$

- Clearance by an organ is determined by blood flow ($Q$) to the organ and extraction ratio ($E$) by the organ
- $E$ is constant for a specific drug, unless the capacity of the organ is saturated by high drug concentration in blood.
- The highest value for $E$ is 1.00 (100%) which equals blood flow to the organ.
Renal Drug Clearance

The three components for renal clearance are:

1. Glomerular Filtration
2. Tubular Secretion
3. Tubular Reabsorption

Over renal Clearance:

\[ \text{Cl}_{\text{renal}} = \text{fu} \times (\text{GFR} + \text{Cl}_{\text{secretion}}) \times (1 - \text{FR}) \]

\( \text{fu} \) = unbound fraction of drug

\( \text{FR} \) = fraction of the drug that is filtered and secreted that is reabsorbed

PORTAL VEIN SYSTEM
First Pass Metabolism of Orally Administered Drugs
Phase 1 Reactions

- Involve one or more oxidations via P450-dependent and P450-independent (mainly alcohol and aldehyde dehydrogenase) systems
- Reductions of NO₂ and keto functions
- Hydrolysis of esters and amides by serum and cellular esterases

Phase 1: P450-Dependent Oxidations

- P450 enzyme families based on sequence identity (animals have 67 families)
- P450 families have greater than 40% sequence identity
- P450 subfamilies have greater than 55% sequence identity (CYP 2 has 8 subfamilies)
- Humans have 57 different P450s
- Major xenobiotic metabolizing families in human are CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4/5
Pre-systemic felodipine metabolism

- CYP3A4 inhibited in enterocyte; $E_\text{i}$ down from 0.7 to 0.1

- Grapefruit juice affects CYP3A4 inhibition
- Systemic level increases 3-fold

**Figure 2.** Sequential pre-systemic felodipine metabolism by CYP3A4 in apical enterocytes of the small bowel (A) and the hepatocytes of the liver (B) in the absence and presence of grapefruit juice. The percent of unmetabolized felodipine is presented before and after passage through the gut wall and the liver. Grapefruit juice selectively inactivated CYP3A4 in apical enterocytes.

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**Phase 2 Conjugation**

**Glucuronyltransferases**
- Cofactor is UDP-glucuronic acid
- Conjugates glucuronic acid to alcohols, phenols, carboxylic acids, amines in β-linkage
- Conjugates can be secreted in the bile
  - Low affinity, high capacity system

**Sulfotransferases**
- Conjugates sulfate to phenols and alcohols: phenols are preferred substrate
- Uses PAPS as cofactor
  - (3′phosphoadenosine 5′-phosphosulfate)
  - Is a high affinity, low capacity enzyme
Metabolism of Codeine

Phase 1

Phase 2

Active drug

Inactive drug

Active drug

Inactive drug

Debrisoquine Phase I Polymorphism

- Expressed as a trimodal distribution of activity (phenotype)
- Reflected in changes in CYP2D6
- 5-10% caucasians and 1% asian population
- Autosomal recessive
- Are greater than 20 mutations identified
Which of the following statements regarding genetic variation in CYP2D6 is correct:

A. Different ethnic groups have different frequencies of both the “poor metabolizer” and “ultra-rapid metabolizer” CYP2D6 phenotypes.
B. The CYP2D6 enzyme is a member of the family of microsomal conjugating enzymes responsible for the Phase 2 metabolism of drugs.
C. The discovery of the CYP2D6 polymorphism is a research breakthrough, but is not clinically relevant because most drugs are metabolized by conjugation.
D. “Ultra-rapid metabolizers” have only one functioning copy of the CYP2D6 gene.
E. “Poor metabolizers” for CYP2D6 are frequently overdosed with cough medicine containing codeine.

Pharmacokinetics

-The study of the concentration time course of drugs and metabolites in vivo.

Important PK Parameters
- Volume of Distribution (Vd)
- Clearance (Cl)
- Half-life (t½)
- Area Under the Curve (AUC)
- C\text{\textsubscript{max}} & T\text{\textsubscript{max}}
- Bioavailability (%F)
Volume of Distribution ($V_d$) of a Drug

$logC_p$ vs. time curve  
Single dose IV

$V_d = \frac{Dose}{C_0}$

Must pay attention to units:

$V_d = (\text{mg/kg})/(\text{mg/L})$

$V_d = \text{L/kg}$

Determining Clearance (Cl)

-Clearance is calculated from a single dose i.v. PK study using the dose and total drug exposure.

Single drug dose i.v., measure $C_p$ as a function of time

$\text{Cl (mL/min/kg)} = \frac{\text{Dose (mg/kg)}}{\text{AUC}_{IV} \text{(mg•min/mL)}}$
Determination of Half-Life ($t_{1/2}$)

The time it takes for a drug in systemic circulation to reduce by half.

- Linear plot: $C_p$ vs. time
- Log plot: $\log C_p$ vs. time

$t_{1/2} = 4$ hr; $C_p$ is cut in half every 4 hr.

Slope = $-k_{\text{elim}}$ (elimination rate constant)

$t_{1/2} = \ln 2/k_{\text{elim}}$

$t_{1/2} = 0.693/k_{\text{elim}}$

Determination of Bioavailability (F)

Drug is dosed IV and by other route (e.g., PO) in different test subjects. IV and PO doses can be, and usually are, different. $C_p$ vs. time data are collected and analyzed for both groups.

Oral Bioavailability ($%F$) = $\frac{AUC_{PO}}{AUC_{IV}} \frac{\text{Dose}_{IV}}{\text{Dose}_{PO}} \cdot 100$
Linear and Non-Linear Pharmacokinetics

- **Linear pharmacokinetics describes the situation where there is a linear correlation between drug dose and drug exposure.**

![Linear PK Graph]

- Almost all clinically used drugs have linear pharmacokinetics
- Predicting increase in exposure from an increase in dose is straight-forward
- Linear PK means all drug elimination processes follow first-order kinetics ($C_p = C_0 e^{-kt}$)

- **Non-linear pharmacokinetics describes the situation where drug dose and exposure are not linearly correlated.**

![Non-linear PK Graph]

- Also called capacity-limited, dose-limited, saturable, concentration-dependent, and/or Michaelis-Menten elimination.
- Undesirable drug property—dose/exposure relationship not straight-forward.
- Usually a result of drug saturation of a metabolic enzyme or transporter involved in the rate-limiting elimination step, but also can result from saturation of an absorption process.
- Drugs in common use have non-linear PK: ethanol, phenytoin, aspirin, amoxicillin
First Order Kinetics Allows Predictability

- Can predict dosing regimen based on therapeutic window $Cl$, $V_d$ and $t_{1/2}$.
- Loading dose
  $$LD = V_d \cdot C_{pss}$$
- At steady state the dose
  $$Dose = Cl \cdot C_{pss}$$

Important Points About Clearance

1. Clearance ($Cl$) reflects “total body clearance” (hepatic and renal and other routes) and the units of $Cl$ are volume/unit time (ie L/hr)
   $$Cl_T = Cl_H + Cl_R + Cl_{other}$$
2. Do not confuse clearance ($Cl$) with elimination rate or half-life. Remember that half-life depends on both the volume of distribution ($V_d$) and clearance $Cl$.
   $$t_{1/2} (hr) = \frac{0.693 \cdot V_d (L)}{Cl (L/hr)}$$
   - $t_{1/2}$ decreases with increasing $Cl$
   - $t_{1/2}$ increases with increasing $V_d$
3. Half-life may not correlate with $Cl$ when comparing two drugs:
   - Alprazolam: $Cl = 4$ L/hr, $V_d = 59$ L, $t_{1/2} = 10$ hr
   - Escitalopram: $Cl = 23$ L/hr, $V_d = 1100$ L, $t_{1/2} = 33$ hr
You have a patient, Robert H, who slipped shoveling snow and had hurt his hip. He has surgery and when he was recovering in the rehabilitation unit he developed sudden pleuritic chest pain; a CT scan revealed a pulmonary embolus. He was treated with heparin and warfarin ($t_{1/2} = 40$ h; $Vd = 0.14$ L/kg; $Cl = 0.045$ ml/min/kg) was started at 5 mg/day with a target international normalized ratio (INR) of 2.0-3. He returned to rehabilitation and after a two weeks his INR was 6.2. He was taking no other medications and so advised him to stop taking warfarin for 2 days. How much would you expect the plasma concentration to decrease at the end of 2 days?

A. By about 15%.
B. By about 25%
C. By about 50%
D. By about 75%
E. By about 95%
It is well established that CYP2C9*1, CYP2C9*2 and CYP2C9*3 have a rank order of \( \frac{V_m}{K_m} \) for warfarin of 100, 75, and 25, respectively. Warfarin is a low extraction ratio drug and as a result you would predict that the steady state concentration of warfarin at the same dose will be:

A. The same for patients that have the different genotypes since protein binding is the same.
B. The patients with the CYP2C9*2 genotype will have a steady state level that is about 75% higher than the patients with the CYP2C9*1 genotype.
C. The patients with the CYP2C9*3 genotype will have a steady state level that is about 25% lower than the patients with the CYP2C9*1 genotype.
D. The patients with the CYP2C9*2 genotype will have a steady state level that is about 25% higher than the patients with the CYP2C9*1 genotype.

You have been asked to explain the differences in the volume of distribution of an experimental drug (X) determined in two laboratories. The only difference between the two is one used plasma (\( V_d = 500 \text{L/kg} \)) and the other used whole blood (\( V_d = 0.7 \text{L/kg} \)). Which is the best explanation for this difference?

A. X is clearly very hydrophobic and distributed to fat.
B. X is bound to plasma albumin.
C. X is weakly bound to red blood cells.
D. X is sequestered in a tissue.
E. X is sequestered in red blood cells.
F. There is not enough information to answer this question.
A comatose patient is admitted to the emergency department 4 hr after an overdose of phenobarbital. The plasma concentration of the drugs at the time of admission is 100 mg/L and the apparent volume of distribution, elimination half-life, and clearance of phenobarbital are 35 L, 4 days, and 6.1 L/day, respectively. The ingested dose was approximately:

A) 1 g  
B) 3.5 g  
C) 6.1 g  
D) 40 g  
E) 70 g

Additional Slides and Questions for Study
Basics of Toxicology

- Supportive care
- Limit absorption
- Enhance elimination

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Limit absorption

- Empty the stomach:
  - Gastric Lavage (GL)
- Block absorption (by adsorbing)
  - Activated charcoal (AC)
- Decrease transit time
  - Cathartics (e.g. sorbitol with charcoal)
  - Whole Bowel Irrigation (WBI)

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Limit absorption

• Toxin is still in the GI tract
  – Pharmacokinetic considerations (e.g. absorption)
  – Pharmacodynamic considerations
    • Slowed GI transit (e.g. antimuscarinics/opioids)
  – Toxicokinetic considerations
    • Exceeding normal absorptive capacity

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Salicylate toxicity

• Respiratory alkalosis
  – Salicylates stimulate the respiratory center
  – Decrease in $pCO_2$
  – Increase in pH
• Metabolic acidosis
  – Uncouple oxidative phosphorylation
  – Decrease in $HCO_3^-$
  – Decrease in pH
• Respiratory usually wins

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Salicylate toxicity

• Typical blood gas:
  – pH = 7.50 / pCO₂ = 10 / pO₂ = 100
• Typical metabolic panel:
  – Na 140, Cl 110, HCO₃ 10
    • Metabolic acidosis
    • Elevated anion gap
      – AG = Na – (Cl + HCO₃)
      – AG = 140 – (110 + 10) = 20
      – (normal AG is < 12 [some say < 8])

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Enhance Elimination

• Now that the toxin is absorbed, can we eliminate it from the body?
  – Alkaline diuresis (ion trapping)
  – Multiple dose activated charcoal (MDAC)
  – Hemodialysis

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Alkaline diuresis (ion trapping)

• What is it?
  – Sodium bicarbonate – bolus then drip
  – Increases the pH of the serum and the urine

• Useful for agents that are weak acids and have substantial urinary elimination
  – Salicylates
  – Phenobarbital

• How does it work?

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Alkaline Diuresis

• Salicylic acid is a weak acid
• pKa 3.5
• Ionized form is in equilibrium with non-ionized form
• Non-ionized form crosses membranes efficiently

(pH=7.4)

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Alkaline diuresis

Salicylate Toxicity – early after ingestion, normal pH

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(from Dr Rob Hendrickson, SPH Management of the Poisoned Patient, 2014)

Alkaline Diuresis

Salicylate Toxicity – before alkalinization, low pH

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(from Dr Rob Hendrickson, SPH Management of the Poisoned Patient, 2014)
Alkaline diuresis

Salicylate Toxicity – after alkalinization, normal pH

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Sal-H → Sal- + H+

(from Dr Rob Hendrickson, SPH Management of the Poisoned Patient, 2014)

Alkaline Diuresis – Does it work?

As urine pH goes from pH 5 to 8, renal clearance increases from 1mL/min to >100mL/min and half-life decreases from 48 hours to 6 hours

\[ t_{1/2} = \frac{0.693 \cdot V_d}{Cl} \]

(from Dr Rob Hendrickson, SPH Management of the Poisoned Patient, 2014)

Acetaminophen Metabolism

Treatment for any suspect acetaminophen overdose is N-acetylcysteine!!!

Sympathomimetic

- Hyperthermia
- Tachycardia
- Hypertension
- Warm/moist skin
- Agitated delirium
  - Seizures
  - Paranoia/hallucinations
  - Agitation

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
### Sympathomimetic

- Hyperthermia
- Tachycardia
- Hypertension
- Warm/moist skin
- Agitated delirium
  - Seizures
  - Paranoia/hallucinations
  - Agitation

**Causes:**
- Cocaine
- Amphetamine
- Phencyclidine (PCP)
- Withdrawal
  - Alcohol
  - Benzodiazepines
  - GHB
  - Barbiturates

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

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### Cholinergic Toxidrome

- Muscarinic
- Nicotinic
- CNS

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Cholinergic Toxidrome

- **Muscarinic:**
  - Diarrhea/diaphoresis
  - Urination
  - Miosis
  - Bradycardia/bronchorhea
  - Emesis
  - Lacrimation
  - Salivation

- **Nicotinic:**
  - Tremor
  - Fasciculation
  - Paralysis
  - *Sympathetic ganglia

- **CNS:**
  - Sedation/confusion
  - Seizures

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Cholinergic Toxidrome

- **Causes:**
  - Pesticides
    - Organic Phosphorous compounds (OPs)
    - Carbamates
  - Nerve Agents:
    - VX, soman, sarin, tabun
  - Pilocarpine, muscarine

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Antimuscarinic Toxidrome

- Muscarinic blockade
- No nicotinic blockade
  - so no major muscular symptoms

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Antimuscarinic Toxidrome

- Hyperthermia (HOT)
- Tachycardia/Hypertension
- Red, hot, dry skin (DRY, RED)
- Mydriasis (BLIND)
- Absent Bowel Sounds
- Urinary retention
- Confusion/hallucinations (MAD)

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Antimuscarinic Toxidrome

• Causes:
  – Atropine/scopolamine
  – Antihistamines
  – Antipsychotics
  – Tricyclic antidepressants
  – Skeletal muscle relaxants

Opioid Toxidrome

• Miosis
• CNS depression
• Respiratory depression

• Causes:
  – Opiates:
    • Morphine, codeine
  – Opioids:
    • Hydromorphone
    • Methadone
    • Meperidine
    • Oxycodone
    • Hydrocodone
    • Fentanyl

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Serotonin syndrome

- Increased serotonin in synapse:
  - Drugs that block serotonin reuptake (e.g. antidepressants [SSRIs, SNRIs], cocaine, fentanyl, bupropion, etc)
  - Drugs that increase serotonin release (e.g. MDMA, amphetamine, cocaine, lithium)
  - Drugs that inhibit serotonin metabolism (e.g. MAOIs, linezolid)

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Calcium channel blocker toxicity

- Bradycardia, AV block
  - Decreased flow through CC => slow phase 0/4

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Calcium channel blocker toxicity

• Hypotension
  – Decreased contractility
  • Less Ca enters the cell -> less Ca release from SR -> less Ca to bind to Trop C -> weaker contraction

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Calcium channel blocker toxicity

• Hypotension
  – Decrease in systemic vascular resistance
  • Ca influx into smooth muscle is required for basal tone and contraction

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
**Calcium Channel Blocker toxicity**

- **Treatments:**
  - For contractility
    - Beta agonists (e.g. dopamine, epi)
    - Insulin

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Calcium Channel Blocker toxicity

- Treatments:
  - For vasodilation –
    - Alpha agonists (e.g. PE, NE, Epi)
    - Calcium

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)

Calcium channel blocker toxicity

- Functional antagonists – a bunch
- No chemical antagonists
  - …waiting for verapamil Fab…
- No receptor antagonists
  - Calcium channel openers –
- Dispositional antagonist - ILE

(from Dr Rob Hendrickson, SPH, Management of the Poisoned Patient, 2014)
Case 1:

RJH is a 69 y/o male with a past history of seizure disorder and gout has been residing at a skilled nursing facility in order to receive intravenous imipenem-cilastatin (a carbapenem) to treat osteomyelitis due to E. coli. During his second week of antibiotics at the facility, he developed a gout flare, for which he self-administered his usual medication prescribed as to be taken as needed, probenecid. Two days later, he suffered a witnessed tonic-clonic seizure.

1. What is the pharmacodynamic target for imipenem-cilastatin?
2. Why are imipenem and cilastatin given together?
3. Describe the factors involved in the renal clearance of a drug?
4. What precipitated the seizure in this patient? Why?

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Major Antimicrobial Targets

1. Cell wall synthesis: penicillins, cephalosporins, **carbapenems**, monobactams, glycopeptides, cyclic lipopeptides, bacitracin
2. Protein synthesis: aminoglycosides, macrolides, clindamycin, tetracyclines, glycyyclines, linezolid, streptogramins
3. Nucleic acid synthesis: fluoroquinolones, sulfonamides, trimethoprim, rifamycins
4. Cell membrane function: polyenes, triazoles, polymixins, echinocandins

(from Dr. Jim Leggett, BLHD 710, 2014)
Cell Wall Synthesis Inhibitors (6)

Carbapenem and Monobactam β-lactam Antibiotics

1. Major pharmacologic properties
   a. Interfere with bacterial peptidoglycan cell wall synthesis, like all β-lactams
   b. Bactericidal (time-dependent, concentration-saturable), like all β-lactams
   c. Adequate concentrations in serum, urine, soft tissues, synovial, pleural, and other fluids. Adequate CSF concentrations in inflamed meninges
   d. Resistant to most β-lactamases except extended-spectrum β-lactamases, called ESBLs (aztreonam) and carbapenemases (imipenem-cilastatin)

(from Dr. Jim Leggett, BLHD 710, 2014)

Cell Wall Synthesis Inhibitors (7)

Carbapenem and Monobactam β-lactam Antibiotics

1. Major pharmacologic properties (cont)
   e. Excreted primarily unchanged by renal secretion
   f. Imipenem/cilastatin – cilastatin prevents imipenem from being metabolized in the kidney by dehydropeptidase I; cilastatin is itself partially metabolized renally (1 hr half-life for both, 70% excreted unchanged). Other carbapenems not as easily hydrolyzed.
   g. Aztreonam – no immunologic cross-reactivity with penicillins and cephalosporins (except possibly ceftazidime – same side-chain); can use even with IgE-mediated hypersensitivity to other β-lactams

(from Dr. Jim Leggett, BLHD 710, 2014)
Cell Wall Synthesis Inhibitors (7)

Carbapenem and Monobactam β-lactam Antibiotics

1. Major pharmacologic properties (cont)
   
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(from Dr. Jim Leggett, BLHD 710, 2014)

Cell Wall Synthesis Inhibitors (8)

Carbapenem and Monobactam β-lactam Antibiotics

2. Chemistry – hydroxyethyl side chain in a trans-configuration; monocyclic beta-lactam
   
   a. Carbapenem – imipenem/cilastatin
   
   b. Monobactam – aztreonam
   
3. Mechanism of action – same as all β-lactams
   
   a. Carbapenems bind primarily to PBP 1 and 2, causing elongation and ovoid shapes, subsequent lysis
   
   b. Monobactams bind primarily to PBP3 (filaments)
   
4. Resistance – same as penicillins and cephalosporins

(from Dr. Jim Leggett, BLHD 710, 2014)
Renal Clearance

Renal Clearance = [Glomerular Filtration(1) + Active Tubular Secretion(2)] – Passive Tubular Reabsorption(3)

Organic anion and cation secretory transporters

Source: Talbot DC, Postlethwaite J: Vander’s Renal Physiology, 7th Edition:
http://www.accessmedicine.com
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β-Lactam Toxicity (2)

Penicillins, Cephalosporins, Carbapenems, Monobactams (shared by all)

1. Hypersensitivity reactions, mediated by antibodies induced by penicillin degradation products (seen with all β-lactams) bound to protein (haptens)
   - Rash, Stevens-Johnson, serum sickness, drug fever
2. Cytotoxic reactions
   - neutropenia, interstitial nephritis
3. Dose dependent – diarrhea and other GI disturbances, CNS toxicity (seizures – especially imipenem, cefepime)
4. Adverse reactions associated with specific drugs
   a. Hypokalemia (piperacillin-tazobactam, due to sodium load)
   b. Platelet function abnormalities (grams of drug – eg piperacillin)

(from Dr. Jim Leggett, BLHD 710, 2014)

Case 2:
BH is a 74 y/o male with a history of a severe penicillin allergy (anaphylaxis) is being successfully treated with dabigatran twice daily for atrial fibrillation. He becomes septic from P.aeruginosa pyelonephritis (infection of the kidney), and he is prescribed gentamicin IV. After 5 days into therapy, the evening nurse reports 20 ml of hematemesis and his creatinine is noted to have gone from 0.9 to 3.4 and his INR was 11.7 compared to 2.4.

1. What are the pharmacodynamic targets for dabigatran and gentamicin?
2. Why was gentamicin selected and given IV?
3. What precipitated the hematemesis in this patient?
4. Would the bleeding have occurred if the patient had been on warfarin instead for his atrial fibrillation?
The Clotting Cascade

Dabigatran

- Orally available but low only about 7%
- Can increase by as much as 75% if taken out of capsule
- Low protein binding, 35%
- Clearance is primarily by glomerular filtration
Protein Synthesis Inhibitors

Aminoglycosides

1. Major pharmacologic properties
   a. Inhibit protein synthesis by binding to bacterial ribosome
   b. Rapidly bactericidal (concentration-dependent)
   c. Excreted renally by glomerular filtration (as unchanged drug)
2. Chemistry – central 6-membered aminocyclitol ring linked to ≥2 aminosugar residues by glycosidic bonds
   a. Examples – gentamicin, tobramycin

(from Dr. Jim Leggett, BLHD 710, 2014)

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Protein Synthesis Inhibitors (2)

Aminoglycosides

3. Mechanisms of action
   a. Primary target 30S ribosome, interfering with peptide chain elongation (protein synthesis)
   b. Other cellular effects – plasma membrane damage, impaired cellular respiration, RNA and DNA synthesis
4. PK parameters for Gentamicin: >90% urine; <10% protein binding

(from Dr. Jim Leggett, BLHD 710, 2014)
β-Lactam Toxicity

Cross-Reactions

1. Penicillin-allergic reactions to other β-lactams
   a. in pcn-allergic patients, cross-reaction is no greater than controls to 2nd, 3rd, 4th generation cephalosporins, carbapenems
   b. no cross-reaction to aztreonam

2. Cephalosporin-allergic reactions to other β-lactams
   a. in IgE-allergic patients, minimal risk of cross-reaction to carbapenems
   b. no cross-reaction to aztreonam (except perhaps with ceftazidime)

(from Dr. Jim Leggett, BLHD 710, 2014)

β-Lactam Toxicity

Introduction

1. Selective toxicity - depends on major differences between prokaryotic and eukaryotic cells (e.g. ribosome, peptidoglycan synthesis)

2. 3 major types of adverse reactions
   a. Direct (dose-dependent toxicity)
   b. Hypersensitivity (variety of allergic, humoral, cellular, immunologic reactions to drugs)
   c. Biologic alteration of host (e.g. antibiotic-associated colitis, uncommon idiosyncratic reactions with no known mechanism)

(from Dr. Jim Leggett, BLHD 710, 2014)
Aminoglycoside Toxicity

Aminoglycosides
Adverse reactions – essentially no hypersensitivity reactions

1. Nephrotoxicity – generally reversible, proximal tubule damage (impaired renal function, electrolyte wasting); limit toxicity by once-daily dosing and short duration
2. Ototoxicity – generally irreversible, rarely a genetic predisposition (hearing, balance loss); AUC-related
3. Neuromuscular blockade – rare, flaccid paralysis (anesthetics, botulism, myasthenia gravis)

(from Dr. Jim Leggett, BLHD 710, 2014)

The Clotting Cascade

Warfarin is highly protein bound and is cleared by hepatic P450 metabolism
The data shown at the left is the iohexol (structure on the right) plasma concentration versus time profile.

Consider the following questions:

1. What was the route of injection in this study?
2. Are the results consistent with a one compartment model?
3. How would you determine iohexol Cl from these data?
4. If you are told that these results can be used to determine the GFR, what assumptions must you make about this compound? What chemical features of iohexol are consistent with these assumptions?
5. If you wanted to experimentally demonstrate that the Cl determined from this study was indeed the GFR what would you need to do?

Is a log concentration vs time plot and based on very high first point would assume is IV

The shape of the curve is not consistent with a one compartment model; a clear distribution phase followed by elimination phase

Can use a noncompartmental model: Cl = Dose/AUC. From small number of points a single compartment is assumed then: Cl = Dose/ (C₀/kₘₐₓ) is being used with dried blood spots (Nephron Clin Pract. (2007) 106:104-112)
Assumptions

• Looks very polar
  lots of OH groups;
  LogP = 0.32
• Is not protein bound
• Is not metabolized
  by the liver
• Is not secreted
• Is not reabsorbed