Pharmacology 101: Pharmacodynamics & Pharmacokinetics

A Review of Pharmacodynamics & Pharmacokinetics with Emphasis on Clinical Application for the Primary Care Provider

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Objectives
- Discuss the concepts of relative potency, therapeutic index, tolerance, tachyphylaxis, desensitization, etc (Rx)
- Recognize how and why side effects (and hypersensitivity) from drugs occur, and how they can impact patients as well as therapeutic goals (Rx)
- Explain the roles of protein binding, drug metabolism and renal elimination in drug disposition and potential drug interactions (Rx)
- Review how drug half-life influences attainment of steady state therapeutic drug levels, titration schedules, dosing regimens and discontinuation and should impact drug selection for any given patient (Rx)

Disclosures
This speaker has no financial or other conflicts of interest to disclose

Pharmacology
From the Greek – Pharmakon
poison or potion

“All things are poisons, for there is nothing without poisonous qualities.
It is only the dose which make a thing a poison

. . . a lot kills, a little cures”
Aureolus Paracelsus (1493 – 1541)
"Grandfather" of Pharmacology

Pharmacodynamics
The fundamental things apply as time goes by . . . .
Basic steps in choosing any medication

1. Safety (in your particular patient)
2. Tolerability
   - What are the likelihoods of side-effects?
   - How serious might they be?
3. Efficacy
   - What is the likelihood of improvement?
   - How important is this?
4. Price
   - Consider the cost-benefit ratio
5. Simplicity
   - (regimen, pre/concurrent labs, etc)

When chosen -

- Consider it a clinical trial of that medication
  - Does it work or not?
  - Is it tolerable?
- If medication does work:
  - Give it for the minimum time possible
  - Frequent monitoring and reviews regarding
    - continuing need
    - possible adverse effects
- If medication does not work (or no longer needed)
  - stop it!

“Relative” Potency

What makes one drug more “potent” than another?

Examples:
- diphenhydramine (25 mg) vs clemastine (1 mg)
- chlortiazide (500 mg) vs haloperidol (25 mg)
- sertraline (50 mg) vs escitalopram (10 mg)
- morphine (30 mg) vs hydromorphone (7.5 mg)

Affinity and / or Intrinsic Activity

Maximal Efficacy
**Pharmacology 101:**
**Pharmacodynamics & Pharmacokinetics**

Why might some drugs in the same class have greater efficacy than others?

[Image of pharmacological classes]

**Drug Safety - Therapeutic Index (TI)**

<table>
<thead>
<tr>
<th>DRUG A</th>
<th>ED&lt;sub&gt;50&lt;/sub&gt;</th>
<th>TD&lt;sub&gt;50&lt;/sub&gt;</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
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</table>

**Protective Index (PI)**

\[ \text{TI} = \frac{\text{LD}_{50}}{\text{ED}_{50}} = 80/20 = 4 \]

\[ \text{PI} = \frac{\text{TD}_{50}}{\text{ED}_{50}} = 50/20 = 2.5 \]

**Narrow Therapeutic Index**

**Examples:**
- warfarin
- phenytoin
- digoxin
- theophylline
- carbamazepine
- valproate
- aminoglycosides
- lithium
- mg sulfate

\[ \text{TI} = \frac{\text{LD}_{50}}{\text{ED}_{50}} = 45/30 = 1.5 \]

**Tolerance**

A change in the responsiveness to a drug, occurring over time due to the continual presence of the drug in the body, that requires an increase in dose to produce the same effects as the original dose.

**Pharmacodynamic Tolerance**

**Reduction in receptor numbers or sensitivity**
- (opioids, barbituates)

**Pharmacokinetic Tolerance**

aka “Drug Disposition Tolerance”
aka “Metabolic Tolerance”
- Drug causes increase in hepatic drug metabolizing enzymes that inactivate the drug.
- carbamazepine, phenytoin
Tachyphylaxis

- Rapid development of tolerance
- Can occur as early as 1st or 2nd dose
- eg. organic nitrates, stimulants

Increased dose doesn’t help
Need time-off from drug

Desensitization

- Rapid decrease in cell responsiveness to drug
- eg. alpha or beta-agonists

Increased dose doesn’t help
Need time-off from drug

Side Effects

- Upset stomach
- Nausea
- Diarrhea
- Constipation
- Dry mouth
- Cough
- Dypsnea
- (minor) Palpitations

Annoying or Nuisance Side Effects Threaten compliance

- Dizziness
- Nervousness
- Drowsiness
- Blurred vision
- Insomnia
- Headache
- Urinary hesitancy
- Urinary frequency

Drug affects multiple targets

- Tricyclic Antidepressants
  - blocks reuptake
  - Intended Target: Depression
  - Additionally Affected: Serotonin, Norepinephrine, Dopamine

Drug formulation cannot be titrated easily

- Amlodipine
  - Blocks calcium channels
  - Side Effects Include:
    - dizziness
    - headache
    - peripheral edema

Dosed:
- 2.5 mg
- 5 mg
- 10 mg
Cosmetic Side Effects
- Hair growth / loss
- Acne
- Rashes
- Weight Gain / Loss
- Stunted growth
- Nystagmus
- etc

Annoying or Nuisance Side Effects
Threaten compliance

Serious / life-threatening SEs
- Chest pain
- Arrhythmias
- Palpitations
- Protracted vomiting or diarrhea
- Difficulty breathing
- Severe headaches
- Fainting
- Seizures or convulsions
- Profound rashes
- Yellowing of the skin or eyes

Hypersensitivity - Drug Allergy
- Uncommon
- No correlation with known pharmacological properties of the drug
- No linear relationship with drug dosage
- Rx range from a mild localized rash to serious systemic complications
- Can affect many organ systems, but the skin (rashes) is most frequently involved
- Risk Factors include: frequent exposure to the drug, large doses, parenteral administration, familial tendency to develop allergies and asthma.

Types of hypersensitivity reactions caused by drugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Immediate, IgE-mediated</th>
<th>Bronchospasm, urticaria, hypotension, angioedema, Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II</td>
<td>Complement-mediated cytolysis</td>
<td>Leukopenia, vasculitis, rashes, interstitial nephritis</td>
</tr>
<tr>
<td>Type III</td>
<td>Immune complexes</td>
<td>Serum sickness, vasculitis, fever, arthralgias, rashes – erythma, SJS, TEN</td>
</tr>
<tr>
<td>Type IV</td>
<td>T cell-mediated reactions</td>
<td>Contact sensitivity, delayed rashes</td>
</tr>
</tbody>
</table>

Drugs most likely to cause allergy

- **Antibiotics**
  - Beta Lactams, sulfa, tetracyclines
- **Antiepileptics**
  - Phenytoin, carbamazepine, lamotrigine
- **DMARDs**
  - Gold salts, penicillamine, chloroquine
- **Sulfonamides and Sulfonylureas**
  - Thiazides, glipizide, glyburide, etc
- **Antiretrovirals**
  - PIs, NNRTIs, NRTIs

Plasma Concentration vs Time

The Divine Comedy about Pharmacokinetic Data

The Male College Sophomore’s Beer Money Bonanza

Plasma Concentration

Time
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**Pharmacokinetics**

Absorption

Achlorhydria due to:
- PPIs, H2 Blockers, Antacids
- Aging
- Hypothyroidism
- H. pylori infection
- Pernicious anemia
- Atrophic gastritis
- Stomach cancer
- Gastric Bypass

May decrease absorption of:
- itraconazole
- cefpodoxime
- ampicillin esters
- dabigatran
- delavirdine
- indinavir
- atazanavir
- nefivnavir
- vitamin B12 / iron salts

May also affect "dissolution" of some dosage formulations
Chemical Interactions

**CALCIUM**
- Tetracyclines
- Quinolones
- Bisphosphonates
- Levothyroxine

**IRON**
- Tetracyclines
- Quinolones
- Bisphosphonates
- Levothyroxine
- Penicillamine
- Levodopa

Plasma Protein Binding

**Albumin**
- Little or no decrease with healthy aging
- Significant decrease with disease & malnutrition
  - Hepatic impairment – hepatitis, cirrhosis, alcoholic liver
- Binds mostly acidic drugs: phenytoin, warfarin, digoxin, NSAIDs, COX2's, lamotrigine, sulfonyleureas, valproic acid

Competition for Protein Binding

**Free drug**
- 100% increase in "active" drug concentrations
Pharmacokinetic Interactions
Protein Binding
Potential interactions between drugs that are highly protein bound
- warfarin
- phenytoin
- valproic acid
- lamotrigine
- glyburide
- glipizide
- glimepiride

Cytochrome P450: Raison d’etre

Cytochrome P450 Overview
Major drug metabolizing enzyme system in the body
- Actually comprised of multiple proteins
- Active site or core of the enzyme system is a heme protein
  a.k.a. “mixed function monooxygenase”
- Reactions require molecular oxygen
- Liver and gut wall have the greatest concentration of P450
- Almost all tissues in the body have some P450 (Lungs, Kidney, Skin, Brain)

Cytochrome P450 Mechanism

Fate of P450 Drug Metabolites
Inactive
- Most drugs become inactive after P450 metabolism
- Examples: warfarin, amlodipine, atorvastatin, lorazepam
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Fate of P450 Drug Metabolites

Equally Active "Active Metabolite"
Examples:
- fluoxetine → norfluoxetine
- sildenafil → N-desmethy1sildenafil
- alprazolam → 4-hydroxyalprazolam
- loratadine → desloratadine (Clarinex)
- venlafaxine → O-desmethylvenlafaxine (Pristiq)
- risperidone → 9-hydroxyrisperidone (Invega)

Fate of P450 Drug Metabolites

More Active
Examples:
- losartan → E-3174 (10 – 40x)
- tamoxifen → endoxifen (1000x)
- oxycodone → oxymorphone (3 – 10x)
- hydrocodone → hydromorphone
- tramadol → M1 metabolite (1000x)

Fate of P450 Drug Metabolites

Activation of "ProDrug"
CYP450 necessary to convert drug to its active form
Examples:
- codeine → morphine
- clopidogrel → active compound (ADP receptor blocker)

Fate of P450 Drug Metabolites

Reactive (Toxic) Metabolite
Examples:
- acetaminophen → hepatotoxic metabolite (N-acetyl-p-benzoquinone imine)

Cytochrome P450

- Humans have 17 families of CYP450 genes – 39 subfamilies
- Three families dedicated to drug metabolism – CYPs 1, 2 and 3
- Remaining 14 families involved in physiological / homeostatic functions – biosynthesis or degradation of:
  - cholesterol
  - bile acids
  - steroid hormones
  - vitamin D3

Cytochrome P450 Isoforms
Clinically Important Aspects of Cytochrome P450 Drug Metabolism

**Induction**
- Elevated levels of Cytochrome P450
- Blockade of hepatic drug clearance

**Pharmacogenetics**
- Variability between patients

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Induction
- reversible increase in enzyme concentration resulting from administration of certain drugs
- potential to increase rate of the “inducing” drug's breakdown
  “Pharmacokinetic or Drug Disposition Tolerance”
- may increase the metabolism of other drugs taken concurrently

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**CYP450 Induction**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4</td>
<td>phenytoin, rifampin, carbamazepine, piroglitazone, efavirenz, nevirapine, St. John’s wort</td>
</tr>
</tbody>
</table>

**CYP1A2**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>clozapine, olanzapine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>duloxetine, mirtazapine</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>furosemide, ranitidine, tizanidine, warfarin(R), caffeine, theophylline</td>
</tr>
<tr>
<td></td>
<td>rifampin, omeprazole, broccoli, brussel sprouts, cabbage, char-grilled meat, tobacco smoke</td>
</tr>
</tbody>
</table>
Inhibition of Drug Metabolism

- Due to two drugs competing for the same enzyme
- Drug with greater affinity typically wins!
- Some drugs get into active site and are slow to dissociate
- Drug that is not metabolized can build up to toxic levels

Cytochrome P450 Inhibition

CYP450 Inhibition

**Substrates**

CYP2E1

- Anesthetics: enflurane, halothane
- Miscellaneous: acetaminophen, ethanol,ISONIAZID

**Inducers**

- Ethyl alcohol
- Whiskey
- Scotch
- Bourbon
- Vodka
- Gin
- Wine
- Beer

Acetaminophen Toxicity

- Glucuronide
- Sulfate
- Glutathione

CYP450 Inhibition

**Substrates**

- Calcium Channel Blockers
- Statins
- Protease Inhibitors
- Benzodiazepines
- Antidepressants
- Hydantoins
- Miscellaneous

**Inhibitors**

- clarithromycin
- erthyromycin
- ketoconazole
-itraconazole
-fluconazole
-ritonavir
-verapamil
-amiodarone
-cyclosporine
-furanocoumarins (grapefruit juice)

CYP450 Inhibition

**Substrates**

- Antidepressants
- Antipsychotics
- Beta Blockers
- Opioids

**Inhibitors**

- paroxetine
- fluoxetine
- bupropion
- ritonavir
- terbinafine
- amiodarone
- quinidine
### CYP450 Inhibition

**CYP2D6**
- **Substrates**
  - Pro-drug Substrates (need activation by CYP2D6)
  - codeine: diminished analgesia
  - tamoxifen: decreased protection
- **Inhibitors**
  - paroxetine
  - fluoxetine
  - bupropion
  - ritonavir
  - terbinafine
  - amiodarone
  - quinidine

**CYP2C9**
- **Substrates**
  - Miscellaneous: phenytion, warfarin, sulfamethoxazole
  - NSAIDs: ibuprofen, diclofenac, naproxen
  - Oral Hypoglycemics: glyburide, glipizide, glibenclamide
  - Angiotensin II Blockers: lisinopril, irbesartan, valsartan, candesartan
- **Inhibitors**
  - fluconazole
  - amiodarone
  - ketoconazole
  - voriconazole
  - miconazole
  - sulfamethoxazole
  - gemfibrozil

### CYP2C19
- **Substrates**
  - PPIs: omeprazole, pantoprazole, esomeprazole, rabeprazole
  - Miscellaneous: clobazam, escitalopram, phenytoin, warfarin (R), voriconazole
- **Inhibitors**
  - omeprazole
  - esomeprazole
  - pantoprazole
  - rabeprazole
  - cimetidine
  - fluoxetine
  - ketoconazole

### CYP1A2
- **Substrates**
  - Antipsychotics: clozapine, olanzapine
  - Antidepressants: duloxetine, mirtazapine
  - Miscellaneous: frovatriptan, ropinirole, tizanidine, warfarin (R)
  - caffeine, theophylline
- **Inhibitors**
  - fluvoxamine
  - ciprofloxacin
  - cimetidine

### Pharmacogenetics and Cytochrome P450
- **Major P450 Isoforms**
  - CYP3A4
  - CYP2D6 - Polymorphism
  - CYP2C19 - Polymorphism
  - CYP2C9 - Polymorphism
  - CYP1A2
  - CYP2E1
CYP2D6
Poor Metabolizers (PM)
- Inheritance of two mutant CYP2D6 alleles
- No enzyme or very poor enzyme activity = impaired metabolism of CYP2D6 substrates
  - Caucasians: 8 – 14%
  - African-Americans: 2 – 3%
  - Hispanic: 4 – 5%
  - Asian: < 1%
  Higher plasma drug level due to decreased drug clearance; exaggerated clinical outcome and increased risk of dose-dependent side effects; may have to lower drug dose

CYP2D6
Ultra-extensive Metabolizers (UEM)
- Inheritance of alleles with duplication or amplification of CYP2D6 genes
- Excessive amount of enzyme expressed, high metabolic capacity
  - Northern Africans: 15 - 30%
  - Eastern Africans: 7 – 12%
  - Saudi Arabsians: 2 – 5%
  - Mediterranean: 7 – 12%
  - Northern European: 2 – 5%
  - Asian Chinese: < 1%

Drugs Metabolized by CYP2D6
Potential Consequences in PMs
- TCAs
- venlafaxine
- fluoxetine
- paroxetine
- haloperidol
- perphenazine
- risperidone
- atomoxetine
- tamoxifen
- dextromethorphan
- Beta Blockers
  - metoprolol
  - carvedilol
- Opioids
  - codeine
  - hydrocodone
  - oxycodone
  - tramadol

Drugs Metabolized by CYP2D6
Potential Consequences in UEMs
- TCAs
- venlafaxine
- fluoxetine
- paroxetine
- haloperidol
- perphenazine
- risperidone
- atomoxetine
- tamoxifen
- dextromethorphan
- Beta Blockers
  - metoprolol
  - carvedilol
- Opioids
  - codeine
  - hydrocodone
  - oxycodone
  - tramadol
Posibly higher than normal drug dose required for efficacy; side effects if metabolites are toxic

Cytochrome P450
CYP2C19 Polymorphism
- Poor Metabolizers
  - 25% Caucasian (Absent ~ 4%)
  - 30% African American
  - 40% to 50% Asian
- May impact effectiveness of Copidogrel

Polymorphisms leading to Black Boxed Warning on Plavix
- Clopidogrel is a pro-drug
  Requies CYP2C19 for activation
- Forms disulfide bound
- ADP
- P2Y12 receptor
- Platelet
- CYP2C19

Clopidogrel
Forms disulfide bound
- ADP
- P2Y12 receptor
- Platelet
Cytochrome P450 CYP2C9 Polymorphism

- Low activity in 3 – 16% of caucasians
- 1 – 4% Asians, ~ 2% African-Americans
- May affect clearance of:
  - Phenytoin, S-warfarin
  - losartan, valsartan, glipizide, glyburide, diclofenac, naproxen, ibuprofen, celecoxib, rosuvastatin, fluvastatin

Summary of non-drug agents that may have clinically relevant impact of drug metabolism

- Diet, Lifestyle, Environment
- P450s can be induced or inhibited by
  - alcohol
  - caffeine
  - constituents of tobacco
  - charcoal-broiled foods
  - cruciferous vegetables
  - grapefruit juice
  - air or water pollutants

Renal Elimination

- For any drug undergoing renal elimination, total clearance is the sum of any or all three of the following:
  - Glomerular Filtration
  - Passive Reabsorption
  - Active Secretion
- Altered Renal Function can affect clearance and require dosage adjustment
Clearance
- Factors affecting renal clearance
  - Disease States
    - Kidney Disease
    - CHF
    - Hypertension
  - Physiological factors
    - Blood Volume
    - Cardiac Output
    - Urine pH
    - NSAIDS

Pharmacokinetic - Renal Elimination
- Some Drugs Primarily Eliminated In the Kidneys that Require Dosage Adjustment
  - Penicillins
  - Aminoglycosides
  - Fluroquinolones
  - ACE Inhibitors
  - Atenolol / Nadolol
  - Lithium
  - Thiazides
  - Metformin
  - H2 blockers (some)
  - Bisphosphonates

Dosing guidelines in renal impairment
- Dosage adjustment guidelines which are based on creatinine clearance (CrCl) have been published
- Manufacturers are now required by FDA to provide dosage guidelines for patients with decreased creatinine clearance
- A dosage regimen may be adjusted either by lowering the dose or prolonging the dosage interval

Renal Impairment Example Dosing

<table>
<thead>
<tr>
<th>Clcr (mL/min)</th>
<th>Total Daily Dose (mg/day)</th>
<th>Dose Regimen (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150</td>
<td>900-3000</td>
<td>300 TID 400 TID 500 TID 600 TID 800 TID 1200 TID</td>
</tr>
<tr>
<td>&gt;30-59</td>
<td>400-1400</td>
<td>200 BID 300 BID 400 BID 500 BID 700 BID</td>
</tr>
<tr>
<td>&gt;15-29</td>
<td>200-700</td>
<td>200 QD 300 QD 400 QD 500 QD 700 QD</td>
</tr>
<tr>
<td>15*</td>
<td>100-300</td>
<td>100 QD 125 QD 150 QD 200 QD 300 QD</td>
</tr>
</tbody>
</table>

*For patients with creatinine clearance <15 mL/min, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 mL/min should receive one-half the daily dose that patients with a creatinine clearance of 15 mL/min receive).

Renal Transporters “Active Secretion”

- Anionic transporter (OAT): furosemide, thiazides, penicillins, NSAIDs, methotrexate, probenecid
- Cationic Transporter (OCT): metformin, contrast media (iodinated), cinetidine, amiloride, morphine, procainamide, quinidine

Return to systemic circulation

Efferent arteriole
Proximal renal tubule

Efferent arteriole
Proximal renal tubule

Anionic transporter (OAT): furosemide, thiazides, penicillins, NSAIDs, methotrexate, probenecid

Cationic Transporter (OCT): metformin, contrast media (iodinated), cinetidine, amiloride, morphine, procainamide, quinidine

Return to systemic circulation

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2018
Elimination:
Clearance & Dosing Considerations

• **Zero order:** constant rate of elimination irrespective of plasma concentration
  - Eg. Alcohol, high doses of aspirin, phenytoin

• **First order:** rate of elimination proportional to plasma concentration. Constant *Fraction* of drug eliminated per unit time

\[
\text{Rate of elimination } \propto \text{Amount} \\
\text{Rate of elimination } = K_{el} \times \text{Amount}
\]

Time to “Steady-State”

- It takes 5 half-lives to reach steady state
- It takes 5 half-lives to reach new steady state following “up” or “down” titrations
- It takes 5 half-lives for drug to be out of body after d/c
- Clinical assessment of a drug’s value should not be made until steady state reached!
- Published half-life will vary depending on patient’s liver, renal function or interactions with other drugs!

Pros & Cons – short vs long $t_{1/2}$

**Short Half-life (< 6 hrs)**
- **Pros**
  - Quick to steady state
  - Quick titrations
  - Quick out after DC
  - Generally less $$
- **Cons**
  - tid – qid dosing
  - Compliance issues
  - Missed dose issue

**Long Half-life (> 18 hrs)**
- **Pros**
  - Bid or daily dosing
  - Less peak-valley issues
    - Stable when at SS
  - Missed dose may not be as much a problem
- **Cons**
  - Generally more $$
  - Accumulation / Toxicity
  - Slow to SS and titrations