**Kinetics of Pharmacologic Response**

**PHARMACOKINETICS vs. PHARMACODYNAMICS**  
It’s all about the response

**Pharmacodynamics** is the study of the kinetics of pharmacologic response at different drug dose/concentrations.

**What the drug does to the body:** *what patients really care about*

Need information on 1. Dose vs. response, and/or 2. Concentration vs. response

**THERAPEUTIC WINDOW**  
A happy medium 😊

Too little: no response, useless 😓  
Too much: unwanted problems 😞

A concentration range in which therapeutic success occurs, where both safety and efficacy are achieved.

MEC < therapeutic window < MTC

**QUANTAL vs. GRADED EFFECTS**

<table>
<thead>
<tr>
<th>QUANTAL</th>
<th>GRADED</th>
</tr>
</thead>
<tbody>
<tr>
<td>All or none</td>
<td>Continuous response</td>
</tr>
<tr>
<td>e.g. Arrhythmia suppression, yes/no</td>
<td>e.g. Blood pressure ↓, quantifiable</td>
</tr>
</tbody>
</table>

**PLASMA CONCENTRATION > DOSE**  
in relation to finding a relationship to effect

*Why, you ask?*

1. **Time matters**  
   Dose is okay for quantal effects (e.g. migraines), not so much for graded effects.

2. **One size doesn’t fit all**  
The same dose can produce different concentrations in different people.

**E<sub>MAX</sub> MODEL**  
Concentration vs. Effect

\[
E = \frac{E_{\text{max}} C^\gamma}{EC_{50}^\gamma + C^\gamma}
\]

nickname the “Hill Equation” (located at the bottom right hand corner of the equation sheet)

\(\gamma = \text{shape factor, usually 1≤}\gamma≤3\)

Describes steepness of slope: ↓\(\gamma\) = ↑linearity of the line

The bigger/steeper the \(\gamma\), the smaller the concentration needed to increase the intensity of effect: we want ↑\(\gamma\)
RESPONSE: ONSET, DURATION, INTENSITY  
What pharmacodynamics is all about!

Onset of effect: when the drug starts to kick in
- Can be described by either $C_{\text{min}}$ or $A_{\text{min}}$
- $C_{\text{min}}$ = minimum effective concentration
- $A_{\text{min}}$ = minimum amount in body, where $A_{\text{min}} = C_{\text{min}} \times V_d$
- Factors that affect time to onset:
  - Route of administration (e.g. po vs. IV)
  - Release of drug from dosage form (e.g. enteric coated)
  - Distribution kinetics of drug into target site (i.e. Vd)
  - Dose of drug

Duration of effect: how long the drug makes you feel good
- The effect lasts as long as the concentration at the site of action is above the minimum effective concentration (i.e. the concentration is still within the therapeutic window)
- Factors that affect duration of effect:
  - Dose of drug
  - Rate of removal of drug from site of action (e.g. clearance, elimination)
- $t_d = \frac{1}{k} [\ln(\text{Dose}) - \ln(A_{\text{min}})]$
- Semi-log plot of $t_d$ vs. dose
  - Linear line
  - Slope=$1/k$
  - x-intercept=$A_{\text{min}}$
  - x-axis: log scale
- Duration increases by a $t_{1/2}$ each time the dose doubles
- How to increase duration:
  - ↑Dose
  - Dose every time the effect wears off (i.e. body reaches $A_{\text{min}}$)
    - After second time, amount in body = Dose + $A_{\text{min}}$

Intensity of effect: how good it works
- As seen in the plot of response vs. time, there are 3 areas corresponding to 3 types of response
**METABOLITES: WHY THEY’RE IMPORTANT**

- **Good guys**: prodrug \( \rightarrow \) active drug as metabolite
- **Bad guys**: drug \( \rightarrow \) toxic metabolite
- **Protector**: the metabolite becomes an inhibitor, stops the parent drug from being metabolized
- **Blocker**: the metabolite blocks a protein from binding to the parent drug

The change in amount of metabolites in the body = Rate of formation – rate of elimination
Metabolites are more polar than their parent drug, therefore \( V_{d(m)} < V_d \)

<table>
<thead>
<tr>
<th>1. IV bolus</th>
<th>2. IV infusion</th>
<th>3. Multiple dosing</th>
<th>4. Oral dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K&lt;&lt;Km</strong></td>
<td><strong>K&gt;&gt;Km</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Formation rate-limited</td>
<td>• Formation-limited</td>
<td>• Metabolite is elimination rate-limited</td>
<td>• First pass effect plays a major role in forming active metabolites</td>
</tr>
<tr>
<td>• True ( t_{1/2} ) is shorter than parent drug, but apparent ( t_{1/2} ) is about the same as parent drug</td>
<td>• Time to reach ( C_{ss} ): determined by ( t_{1/2} ) of drug</td>
<td>• Time to reach ( C_{ss} ): determined by ( t_{1/2} ) of metabolite</td>
<td>• High ( E_{Hi} ) drugs: significant first pass effect</td>
</tr>
<tr>
<td>• Most drugs</td>
<td></td>
<td>• Principle of superposition: metabolite concentration estimated from conc. vs. time profile</td>
<td>• Metabolites: parent drug concentration <strong>ratio is higher</strong> in dosing than in IV dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \left[ \frac{AUC(m)_{single ~ dose},0\rightarrow \infty}{t} \right] )</td>
<td>• Need higher doses for oral than IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Note how this differs for prodrugs (where the metabolite is the active drug)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Fraction</strong> of dose converted to metabolites is <strong>same</strong> after both IV and oral administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Detection of pharmacokinetic changes after oral dose:</td>
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<td></td>
<td>By looking at the AUC, what situations caused the changes in B vs. A?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Since the slope of the curves are identical but just shifted down, there is reduced F due to incomplete dissolution, but the <strong>proportion</strong> of bioavailable drug converted to metabolites is equal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Since the slope of the metabolite curve is equal to that of the parent drug, there is an ↑ metabolic CL (more metabolites formed), so the enzyme was induced.</td>
</tr>
</tbody>
</table>
Chronic Kidney Disease

Creatinine clearance: how much creatinine is in the urine → our way of measuring GFR (i.e. kidney function)

Cockcroft-Gault equation:

\[ eC_{CR} = \frac{(140 - \text{Age}) \times \text{Mass \ (in \ kilograms)} \times 0.85 \ \text{if Female}}{72 \times \text{Serum Creatinine \ (in \ mg/dL)}} \]

When should we be concerned about a patient?

- When there is a moderate decrease in GFR: <60 ml/min
- (Kidney failure is when GFR < 15 ml/min)
- When comorbidities exist: 1. Diabetes, 2. Hypertension, 3. Hepatitis C

Why should we be concerned?

- Many drugs are renally eliminated, therefore ↓kidney function = ↓CL = ↑drug concentration = ☹️
- Possible problems: ↑side effects, ↑metabolite concentration, ↑drug toxicity
- Problems with the kidney = problems with ADME

What should we consider when planning drug therapy?

- Acute or chronic? How bad is the kidney?
- Age, other diseases, state of other organs

What affects absorption and bioavailability (F)?

- GI emptying can both ↑↓F
- GI tract edema can ↑F
- ↑Gastric pH can both ↑↓F (depends on drug pKa)

What affects distribution?

- Edema (e.g. ascites): bigger tub to fill
- Lots of water in the body means ↑Vd for H₂O soluble drugs
- Higher Vd = lower plasma concentration
- Protein binding
  - CKD patients alter their diet and ↓protein intake
  - ↓Albumin = ↑free drug (fu) = ↑metabolites = possible TOXICITY
  - Highly bound acidic drugs have impaired receptor site binding: acidic drugs compete with free acidic proteins that are eliminated
  - Phenytoin: look at free levels, not total drug levels
  - Warfarin: watch INR closely

What affects metabolism?

- CKD can ↓metabolism by up to 71%
- Causes ↑drug conc. and ↑metabolite conc. = TOXICITY
- Phase I metabolism: biotransformation: hydrolysis, reduction, oxidation (cytochrome P450)
- Phase II metabolism: conjugation
  - Induction: ↓effectiveness
  - Inhibition: ↑toxicity

What affects elimination?

- Need to be worried if renal elimination ≥30%
- Stage of renal insufficiency
- How much urine produced
  - If patient can still urinate but doesn’t eliminate toxins, then ↓fluid in body = ↑drug conc. = TOXICITY
  - Do NOT use nephrotoxic drugs if still urinating, try to preserve kidney function

Half life

- Only used to predict Cₚₚ
- Can reflect a change in Vd and/or CL

Dose adjustments

- ↑Interval + ↓Dose
  \[
  \text{(Usual CL)/(Pt’s CL)} = \frac{(\text{Usual maintenance dose})}{(\text{Modified maintenance dose})}
  \]
Why we matter: how pharmacists impact patient care

- Optimize dosing to achieve optimal efficacy: ↑efficacy + ↓toxicity
  - Renal dosing
  - Weight-based dosing
- Minimize drug toxicity
- Selecting drugs: different people = different drugs: age, organ function, drug interactions, etc.

\[
C_0 = \frac{Dose}{V_d} \quad t_{1/2} = \frac{0.693 \cdot V_d}{K} \quad C = C_0 \cdot e^{-Kt} \quad K = \frac{\Delta \ln C}{\Delta t} = \text{slope of ln(conc) vs. time plot}
\]

For 2 compartment model drugs (i.e. varying tissue distribution),

- Longer distribution phase
- Longer elimination t\(_{1/2}\)
- Need to sample drug in the elimination phase, not the distribution phase
- Example: digoxin

For patient’s with ↓albumin taking drugs that are highly bound,

- Need to adjust calculations based on protein concentration
- Even though the measured drug concentration is too low, with adjusted calculations based on hypoalbuminemia might mean the level is normal
- Example: phenytoin

For drugs with a short t\(_{1/2}\),

- Need continuous infusion
  - Examples: dopamine, epinephrine, norepinephrine, nitroglycerin

For drugs with a long t\(_{1/2}\),

- Need continuous infusion + loading dose
  - Examples: furosemide, procainamide, verapamil, lorazepam, labetalol, diltiazem
Pharmacogenetics vs. Pharmacogenomics
- single gene
- multiple genes

Not everyone is created equal!
How it all started: 1956 the discovery of glucose-6 phosphate dehydrogenase polymorphism

Central dogma: DNA strand → RNA → protein

SNP: Single Nucleotide Polymorphism
- When looking at the “wild type” (normal gene) vs. the “variant” (mutated gene), only 1 nucleotide (G,A,T, or C) is substituted by another
- However! It’s not always a problem: since more than 1 codon codes for each amino acid (redundancy), it might not change a thing and we wouldn’t even notice

The BIG picture
Mutations in the allele can cause changes in proteins that play important roles in drug metabolism, which affects both pharmacokinetics and pharmacodynamics, which affects drug efficacy and/or toxicity

1. Drug metabolizing enzymes
Variants of CYP2C9 (e.g. *2 and *3) causes significant ↓enzyme activity = ↓drug metabolism = ↑drug conc. = TOXICITY
Example: Warfarin: CYP2C9*2 = ↓drug metabolism = ↑drug conc. = ↑INR = ↑risk of bleeding = 😞
Example: 6-mercaptopurine
- 6-mercaptopurine→thioguanine→breaks down blood cells that are cancerous
- However, 6-mercaptopurine also →inactive metabolites via the enzyme TPMT
- If a variant causes ↓TPMT, then the process will be shunted: 6-mercaptopurine→↑thioguanine = anemia
- Fixing the problem: ↓dose for patients with TPMT variant allele

2. Drug transporter proteins
P-gp: a ubiquitous membrane-bound transporter that pumps drugs out which ↓effects (in particular, cancer drugs)
If there’s a defect in P-gp, then more drug is absorbed than normal → too much → TOXICITY
Example: digoxin
- ABCB1 is a gene that codes for the transporter protein P-gp
- Variant causes ↓ABCB1 = ↓P-gp = ↑digoxin concentrations

3. Drug target proteins: receptors, enzymes, intracellular signaling proteins
Only affects pharmacodynamics
Example: Warfarin
- Vitamin K activates clotting factors which reduces bleeding
- Warfarin inhibits Vit K epoxide reductase, which makes Vit K, so ↓Vit K = ↓clotting factors = thinner blood
- CYP2C9 metabolizes warfarin
- VKORC1 is the gene that encodes part of Vit K epoxide reductase
- A SNP (mutation) in VKORC1’s promoter region ↓gene expression = ↓VKORC1 = ↑warfarin conc. = TOXICITY
- Fixing the problem: need to ↓warfarin dose, otherwise patients might bleed too much
- IWPC: Int’l Warfarin Pharmacogenetics Consortium: came up with a dosing equation (available online)
Example: SJS Stevens Johnson Syndrome
- “Toxic epidermal necrolysis” (TEN)
- When taking carbamazepine causes a serious adverse reaction of skin blistering (sometimes fatal!)
- Many Asians have a variant of the HLA gene (B*1502), which ↑risk of SJS from carbamazepine
Drug Interactions

DR. KATZ

The effect one drug has on another: coconspirators or saboteurs

**Alert! Alert!**

- Narrow therapeutic window
- Steep slope on Concentration vs. Effect curve
- Significant first pass metabolism
- Single, inheritable route of elimination occurs
- Warfarin: interacts with NSAIDS, sulfa drugs, macrolide/quinolone antibiotics, phenytoin
- ACE inhibitors: K⁺ supplements, amiodarone, verapamil
- Theophylline: quinolone antibiotics
- Physical incompatibilities
- Chemical interactions
- Inactivation of 1+ drugs

**Pharmacodynamic interactions:**

- Synergy: Drug A ↑ Drug B activity
- Antagonism: Drug A ↓ Drug B activity
- Additive: Drug A + Drug B = 2x conc. = toxicity
- Sequence- or schedule-dependent: time matters! Should Drug A or Drug B go first?

**Common examples pharmacists should be aware of:**

- NSAIDS displace warfarin from protein binding sites = warfarin conc. = bleeding
- ACE inhibitors (e.g. spironolactone) ↓ aldosterone = ↓ K⁺ excretion = hyperkalemia ↑ [K⁺]
- Alcohol + opioids + sedatives = CNS depression (additive)
- Antidepressants + antipsychotics + antihistamines = anticholinergic effects (additive)
- NSAIDS ↑ bp and (-) ACE inhibitors = hypertension (antagonistic)

**Altered ADME**

- Competition for same metabolic pathway
- Saturated pathways
- Neither drug fully metabolized → ↑ drug concentrations → TOXICITY → 😞
- Absorption in the stomach depends on food and pH
  - Full stomach → ↓ GI emptying → ↓ absorption
  - Al³⁺ combines with some tetracycline antibiotics which ↓ GI absorption
  - Foods/drinks ↓ effectiveness of bone drugs (bisphosphonates)
- Metabolism is usually mediated by CYP450’s
  - Inhibitors will ↑ drug concentration = TOXICITY
  - Examples: quinolone antibiotics, H2 blockers,azole antifungals, isoniazid, ritonavir, clarithromycin (think: cip, cim, con, INH, rit, clar)
  - Inducers will ↓ drug concentrations = SUBTHERAPEUTIC
  - Example: St. John’s wort induces P540 = ↓ indinavir = HIV resistance
  - Examples: carbamazepine, phenobarbital, phenytoin, rifampin (think: carb, barb, pheny, rif)