Pharmacokinetics, Pharmacodynamics: Getting Back to Basics in Choosing and Prescribing Medications

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Objectives

● Upon completion of the learning activity the participant will be able to:
  − Identify the basic principles of drug absorption, distribution, and elimination and their relationship to clinical pharmacokinetics.
  − Describe select pharmacodynamic (PD) principles as these apply to safe prescribing.

Objectives

(continued)

● Upon completion of the learning activity the participant will be able to:
  (cont.)
  − Recall the importance of cytochrome p 450 and other influences in drug interactions.
  − Explain the importance of the aforementioned parameters used to design a safe plan of pharmacologic care.

Key Pharm Principles

Pharmacology Defined

● The study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.
  − Source: Katzung, 2012

Pharmacodynamics (PD)

● Study of biochemical and physiological effects of drugs
  − What the drug does to the body and/or disease
Pharmacodynamics
True or false?
● The pharmacodynamic profile of a medication is unchanged over the lifespan.

Pharmacokinetics (PK)
● What the body does to the drug
● Includes
  – Absorption
  – Distribution
  – Biotransformation (metabolism)
  – Excretion of drugs

Pharmacokinetics (PK)
True or false?
● Age and gender significantly impact a medication’s pharmacokinetics.

Fick’s Law
● The tendency for molecules to move in the direction from higher concentration to lower concentration via random molecular motion
● Typically occurs across a membrane or other permeable barrier

Examples of These Permeable Membranes
● Blood-brain
● Mammary
● Placenta
● Cell membrane
● Vessels

Absorption Principles
● Passive diffusion
  – From area of higher to lower concentration
  – Most common form of drug diffusion
Absorption Principles

Why can't the following drugs be given orally?

- Even if you could protect the medication from stomach acid...
  - Unfractionated heparin
    - MW=40,000-50,000 d
  - Insulin
    - MW=5,500 d
  - LWMH
    - MW=8,000 d

For Oral Drug Absorption

- Proper molecular weight
  - <1000, most 250–600 daltons
- Lipid soluble substance
  - To pass through gut wall

For Oral Drug Absorption (continued)

- Small intestine functional
  - Due to large surface area, major point of GI absorption

T ½

- Time required for the amount of drug in the body to be reduced by ½
  - 3-5 T ½ needed to reach steady state
  - 3-5 drug-free T ½ needed to eliminate drug from body

What % is left of original drug dose?

- 1 T ½
  - 50% left
- 2 T ½
  - 50% of 50%=25% left
- 3 T ½
  - 50% of 50% of 50%=12.5% left
- 4 T ½
  - 50% of 50% of 50% of 50%=6.25% left
- 5 T ½
  - 50% of 50% of 50% of 50% of 50%=3.125% left

True or false?

- The T ½ of a medication is a predictable number regardless of the patient’s age, gender, and overall state of health.
### T ½ (hours)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>T ½ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon (Sonata®)</td>
<td>1</td>
</tr>
<tr>
<td>Zolpidem (Ambien®)</td>
<td>2.5</td>
</tr>
<tr>
<td>Triazolam (Halcion®)</td>
<td>T ½</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta®)</td>
<td>T ½</td>
</tr>
<tr>
<td>Temazepam (Restoril®)</td>
<td>T ½</td>
</tr>
<tr>
<td>Estazolam (Prosom®)</td>
<td>T ½</td>
</tr>
<tr>
<td>Quazepam (Doral®)</td>
<td>38</td>
</tr>
<tr>
<td>Flurazepam (Dalmame®)</td>
<td>110</td>
</tr>
</tbody>
</table>

All brand names are the property of their respective owners.

Dose Equiv (mg) | T ½ (h)
--- | ---
Alprazolam (Xanax®) | 0.5 | 6-20
Chlordiazepoxide (Librium®) | 10 | 30-100
Clonazepam (Klonopin®) | 0.25 | 18-50
Clorazepate (Tranxene®) | 7.5 | 30-100
Diazepam (Valium®) | 5 | 30-100
Lorazepam (Ativan®) | 1 | 10-20
Oxazepam (Serax®) | 15 | 8-12


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### Does drug effect exceed 3-5 T ½?
- **Aspirin**
  - T ½ = 0.25 h
  - Effect on platelet function
    - 8-9 d

### Clinical Examples
- **Levotyroxine**
  - T ½ = 7 d
  - 5 T ½ = 35 d
  - When is TSH checked after dose change?
- **Penicillin**
  - T ½ = 1-2 h
  - 5 T ½ = 5-10 h

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### Area Under the Curve (AUC)
- Area under the plot of drug plasma concentration against time after a single dose drug administration

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### Tmax, Cmax
- **Tmax**
  - Time to maximum drug level observed
- **Cmax**
  - Maximum or peak concentration of a drug observed after its administration
  - Clinical significance?
Immediate vs. Sustained Release Morphine

Insulin PK Curves
What is potential problem when insulin is at Cmax?

You see a woman with a chief complaint of dysmenorrhea.

- You can give her one, dose appropriate tablet of any of the following. Which is the best choice?
  A. Naproxen (Naprosyn®)
  B. Naproxen sodium (Aleve®, Anaprox®)
  C. Enteric coated naproxen

In Healthy Volunteers

- Time to Cmax of naproxen forms
  - Naproxen sodium=1 h
  - Naproxen=1.9 h
  - EC naproxen=4 h

How Drugs Cross Cell Membranes

- Passive diffusion
  - Across the gradient
  - Water-soluble via aqueous channels in cell membrane
  - Lipid-soluble through the membrane itself

How Drugs Cross Cell Membranes (continued)

- Active transport
  - Active movement of a drug or ion across a membrane against its concentration gradient. This requires energy, is saturable, and is affected by competitive inhibitors.
Clearance

- Volume of body fluid from which the chemical is completely removed by biotransformation and/or excretion
  - Renal clearance = Water soluble
  - Hepatic clearance = Fat soluble

What does the body want to do to drugs?

- Hang on to these foreign substances?
- Get rid of the “invader” as quickly as possible?

Biotransformation Sites

- Primary
  - Liver
- Less active but clinically important
  - GI tract
  - Lung
  - Skin
  - Kidney

Biotransformation

- Metabolism (biotransformation)
  - The process by which the body modifies or alters the chemical structure of the drug
    - Often to allow for urinary excretion
  - Prodrug (inactive compounds) is transformed to active metabolite.

Medications

Prodrug to Active Metabolite

- Amitriptyline ---> nortriptyline
- Codeine ---> morphine
- Primidone ---> phenobarbital
- Valacyclovir ---> acyclovir
- Heroin ---> morphine
- Levodopa ---> dopamine

Role of Hepatic Function and Drug Metabolism

- Will hepatic impairment potentially lead to:
  - Elevated drug levels?
  - Reduced levels of active metabolites?
First Pass Effect

- Biotransformation and/or excretion of oral drug by hepatic mechanisms prior to entering GI tract are transported to interact with receptors in target tissues.

First Pass Effect (aka Pre-systemic Elimination) (continued)

- Drugs absorbed from the GI tract pass through the portal venous system then through the liver and finally into the systemic circulation.
- Extensive hepatic metabolism/extraction result in minimal drug delivery to the systemic circulation for certain agents.

First Pass Effect (continued)

- Drugs with large first pass effect exhibit significant differences in pharmacological effects comparing oral vs. IV administration.

Compare Oral vs. Parenteral Dose

- Sumatriptan
  - Oral
  - Parenteral
- Levoﬂoxacin (CAP dose)
  - Oral
  - Parenteral

True or false?

- Regardless of route of administration, all medications undergo first pass effect.

Bioavailability

- Percent of dose enter systemic circulation after administration of a given dosage form
  - Lower bioavailability
    - Lovastatin
  - Higher bioavailability
    - Atorvastatin
Statin vs. Statin
McTaggart F, et al.
Am J Cardiol. 2001;87(suppl):28B-32B.

<table>
<thead>
<tr>
<th>Statin Type</th>
<th>T ½</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>20 h</td>
<td>20%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1-2 h</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>14 h</td>
<td>14%</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>1-2 h</td>
<td>24%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1-2 h</td>
<td>17%</td>
</tr>
</tbody>
</table>

Lipophilic vs. Hydrophilic

- Most drugs are designed to be lipophilic to allow for absorption and cell membrane penetration.
- These products must be changed to a hydrophilic metabolite to allow for excretion.

CYP450 Drug Metabolism

- The major process in which drugs are converted from lipophilic to hydrophilic
- This is also a common source of drug-drug interactions.

Biotransformation Sites Via CYP 450

- Liver
- Kidney
- Placenta
- Lung
- Plasma
- Intestinal mucosa

Cytochromes P450 (CYP)

- Important to drug metabolism
  - CYP1A2
  - CYP2C9
  - CYP2C19
  - CYP2D6
  - CYP2E1
  - CYP3A4
- A source of pharmacokinetic DI
Proportion of Medications Metabolized by Select CYP450 Isoenzymes

CYP 1A2
15%

CYP 2C9/19
13%

CYP 2D6
25%

CYP 3A4
47%

Katzung, 2012.

Drug Interactions: Malpractice Trigger!

● CYP 450 Drug-metabolizing isoenzymes: A potential source of drug-drug interactions

Definition Clinical example
Inhibitor | Block the activity of the isoenzyme, limiting substrate excretion, allowing increase in substrate levels, and possible risk of substrate-induced toxicity

| Substrate | Clinical example |
| Substrate | CYP 450 3A4 substrates: Sildenafil (Viagra®), atorvastatin, simvastatin, venlafaxine (Effexor®), alprazolam (Xanax®), others |

Does the “no statin with grapefruit juice” warning extend to all in the class?

CYP450 Substrates

● CYP450 3A4
  – Atorvastatin
  – Lovastatin
  – Simvastatin

● CYP450 2C9
  – Pitavastatin
  – Rosuvastatin

● Not metabolized by CYP450
  – Pravastatin
Caution: DI of Select Statins and Clarithromycin

- “Clarithromycin significantly (p < 0.001) increased the AUC and Cmax of all 3 statins (atorvastatin, lovastatin, simvastatin {CYP 3A4 substrates}), most markedly simvastatin (approximately 10-fold increase in AUC)...”

### CYP450 3A4 Inducer

- St. John’s wort
  - Cyclosporine
    - Result- Transplanted organ rejection
  - Digoxin
    - Decreased digoxin levels by day 10

- Indinavir (many other antiretrovirals)
  - AUC decreased by 57%
  - Extrapolated 8-h trough by 81%
  - Result
    - Increased HIV viral load

### St. John’s Wort: CYP3A4 Inducer

- Indinavir (many other antiretrovirals)
  - AUC decreased by 57%
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  - Result
    - Increased HIV viral load

“But that St. John’s wort really works”...

- St. John’s wort
  - States the 70 yo man with heart failure who is taking digoxin.
  - Has been taking two capsules of St. John’s wort per day for the past 5 years with no evidence of loss of digoxin effect.

“But that St. John’s wort really works...” (continued)

- What advise should you give?
  1) Stop the St. John’s wort immediately.
  2) Taper the St. John’s wort over the next 2 weeks.
  3) Continue to take the St. John’s wort with certain additional advice.
CYP450 Substrates

- CYP450 3A4
  - Atorvastatin
  - Lovastatin
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- CYP450 2C9
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  - Rosuvastatin
- Not metabolized by CYP450
  - Pravastatin

CYP1A2

- 70 year-old woman with UTI
  - On ciprofloxacin
    - CYP 1A2 inhibitor
  - Feeling better but cannot sleep
  - “The antibiotic is keeping me awake.”
    - Drinks 4-5 cups of coffee per day
      - Caffeine=CYP 1A2 substrate

Chemical/Pharmacokinetic DI

- 48 year-old woman with IDA
- Taking oral ferrous sulfate
  - Develops UTI
  - Placed on oral ciprofloxacin
    - Remains symptomatic at 72 hours into treatment
    - Results=Urine culture + E. coli sensitive to ciprofloxacin

Inactivation of Antimicrobial Effect Via Chelation

- Fluoroquinolones
  - All –floxacin suffix antimicrobials
  - 60-70% reduction in –floxacin dose
    - When taken with metals such as iron, calcium (potential with dairy products), magnesium, aluminum
    - Separate in stomach from metals by =>2 hours
      - Ciprofloxacin PI

Other Antimicrobials

- Tetracycline forms including doxycycline, minocycline
  - When taken with metals such as iron, calcium (potential with dairy products), magnesium, aluminum
  - Separate in stomach from metals by =>2 hours

Decreased Absorption when Taken with Food

- Digoxin
  - When taken with high fiber food
    - Wheat bran, rolled oats, sunflower seeds
    - Separate by >2-4 h or consistently take w/above
- Bisphosphonates
  - When taken with any liquid other than water or with food
Increased Absorption when Taken with Food

- Nitrofurantoin (Macrodantin®, Macrobid®)
  - 200-400% increase due to delayed emptying, increased time to dissolve
- Sertraline (Zoloft®)
  - ~33% increase in dose absorbed

Special Considerations Enteral Feedings

- Contains Ca+, other metals, protein
- Binds to components of feeding
  - Potential decrease absorption
  - Chelation

Special Considerations Enteral Feedings (continued)

- Phenytoin suspension
  - 71.6% dose absorption reduction w/ continuous feeding
    - If continuous feeding required, increase dose accordingly
- FQ antimicrobials
  - 27-67% reduction in mean bioavailability

Questions? Comments?

Resources


End of Presentation!
Thank you for your time and attention.

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