Important Concepts

- Pathology: Study of Disease
- Pathophysiology
  - Patho: suffering, disease
  - Physiology: function of body
  - Normal
  - Disease

Development of Disease

- Etiology
- Pathogenesis
- Manifestations

Etiology

- Inherited or familial
- Congenital
- Toxic
- Infectious
- Traumatic
- Degenerative

Pathogenesis

- Natural History

Manifestations/Clinical Features

- Morphology
- Subclinical
- Symptoms
- Signs
  - Lesion
- Sequela(e)
- Complications
- Resolution
Important Concepts Cont
• Drug, Prodrug
• Pharmacology
• Pharmacotherapeutics
• Effectiveness
• Safety: Therapeutic Range and Index
• Selectivity
• Reversible action
• Predictability
• Administration

Important Concepts Cont
• Interactions
• Cost
• Chemical Stability
• Name: Generic, Trade, Chemical, Experimental
• Therapeutic Objective

Intensity of Drug Response
• Administration
  – Route
  – Medication errors
  – Patient Compliance
• Pharmacokinetics
  – Absorption
  – Distribution
  – Metabolism
  – Excretion

Intensity of Drug Response
• Pharmacodynamics
  – Drug-receptor interaction
  – Patient's functional state
  – Placebo effects
• Individual Variation
  – Physiologic variables
  – Pathologic Variables
  – Genetic variables
  – Drug interactions

Nursing Responsibilities (the pitcher and the catcher)
• Pre-administration assessment
  – Baseline data
  – Stratification of risk
• Planning and Implementation: Dosage and Administration
  – Five (hundred) Rights
  – Understand the correct dosing range
  – Appropriate safety measures

Nursing Responsibilities
• Evaluating and Promoting Therapeutic Effect
  – Evaluating Therapeutic Response
  – Promoting compliance/adherence
  – Implementing non-drug measures
• Minimize Adverse Effects
• Minimize Adverse Interactions
• PRN decisions
• Managing Toxicity
• Patient education
Approval of Drugs: Drug Legislation

- 1906: A drug must be what it says it is
- 1938: Drugs must be tested for safety and approved by FDA
- 1962: Drugs must be effective for what they claim: testing procedures
- 1970: Controlled Substances Act
- 1992: Relaxed procedures for Cancer and AIDS drugs
- 1997: FDA Modernizing Act
  - Fast track for AIDS, cancer, and other life threatening conditions
  - Manufacturers must give 6 month notice before discontinuing a drug
  - FDA can require testing in children
  - Clinical trial database
  - Drug companies can provide physicians with articles on “off-label” uses

Drug Approval: Process

- Preclinical testing
  - Toxicity
  - Pharmacokinetics
  - Possible Useful Effects
- Clinical Testing (in Humans)
  - Phase I: Normal subjects; metabolism and side effects
  - Phase II: Patients, therapeutic utility and dosage range
  - Phase III: Patients; safety and effectiveness
  - Conditional Approval
  - Phase IV: Postmarketing Surveillance
- Limitations of Process
  - Women and children
  - Failure to detect all adverse effects

Drug Names

- Chemical (N-acetyl-para-aminophenol)
- Generic (acetaminophen)
- International name (paracetamol)
- Trade Name (Tylenol)

Trade (Brand) Name Problems

- Easier to remember
- Frequent Emotional allusions
  - Viagra
  - Abilify
- Multiple trade names for one drug
- Same trade name with more than one product

Availability

- OTC
- Legend
- Scheduled
  - V: Least dangerous & addictive (Lomotil)
  - IV: Less D&A (Ambien, Xanax)
  - III: D&A: hydrocodone, codeine
  - II: highly D&A: morphine, cocaine
  - I: dangers outweigh benefits: marijuana, heroin

Ways to cross a cell membrane

- Channels and Pores
- Transport systems
- Direct penetration of membrane – must be lipid soluble
  - Polar molecules
  - Ions
Pharmacokinetics

• Absorption – movement of drug from site of administration to blood
  – Rate of dissolution
  – Surface area
  – Blood flow
  – Lipid solubility
  – pH partitioning
• Distribution
• Metabolism
• Excretion

Absorption: Routes of Administration

• Enteral – gastrointestinal (mouth, rectum, tubes)
• First Pass Effect
• Parenteral – injection (IM, IV, SC)
• Topical
• Transdermal
• Inhaled
• Vaginal

Drug Distribution

• Blood flow to tissues
• Exiting the Vascular system
  – Typical Capillary Beds
  – Blood-Brain Barrier
  – Placental Drug Transfer
  – Protein Binding
  – Entering Cells

Metabolism

• Hepatic Drug-Metabolizing System
  • P450 cytochrome system
    – hepatic microsomal enzyme system
  • Therapeutic Consequences of Drug Metabolism
    – Accelerated Renal Drug Excretion
    – Drug Inactivation
    – Increased Therapeutic Action
    – Activation of prodrug
    – Increased or Decreased Toxicity

Metabolism

• Considerations
  – Inductions of P450 system
  – Competition between drugs
  – First Pass Effect
  – Nutritional status

Example P450 Drugs

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Induction</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>CYP2C3</td>
<td>CYP2A6</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>CYP2C19</td>
<td>CYP2A6</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>CYP3A4</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>UGT</td>
<td>CYP2B6</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>CYP2C19</td>
<td>CYP2A6</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>CYP2C19</td>
<td>CYP2A6</td>
</tr>
<tr>
<td>Primidone</td>
<td>CYP3A4</td>
<td>CYP2A6</td>
</tr>
<tr>
<td>Topiramate</td>
<td>CYP2C19</td>
<td>β-oxidation</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>β-oxidation</td>
<td>CYP2C19 UGT</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>CYP2A6</td>
<td>CYP2A6</td>
</tr>
</tbody>
</table>

UGT = uridine diphospho-glucuronosyltransferase.
Drug Excretion

- Removal of Drug from the body (urine, sweat, bile, saliva, breast milk, lungs)
  - Renal Drug Excretion
    - Glomerular Filtration
    - Passive Tubular Reabsorption
    - Active Tubular Secretion
  - Breast Milk
  - Bile

Renal Function

- Serum Creatinine levels
  - Produced at constant rate by muscle
  - Excreted at constant rate by kidneys
  - Unreliable in "elderly"
- Creatinine Clearance
  - 24 hour urine
  - Estimated
    - Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)
    - Sex: Male = 1; Female = 0.85

Pharmacogenetic Testing (PGx)

- Predicting drug response based on patient's genetic profile
- Largely determined by
  - P450 enzymes (metabolism)
  - Transporter Mechanisms
    - Absorption
    - Distribution
    - Excretion
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791676/

Pharmacodynamics

- Dose – Response Relationships
  - Maximal Efficacy
  - Potency
- Drug – Receptor Interactions
  - Receptor-Types
  - Selectivity
  - Theories
  - Mode of Action

Dose Response

Maximal Efficacy
Potency

Mode of Action
- Agonists
- Antagonists
- Partial Agonists
- Regulation of Sensitivity
- Selectivity
- Lock and key

Example of Receptor Selectivity

Drug Interactions
- Drug-Drug Interactions
  - Intensification: Effect and/or Adverse Effects
  - Reduction
- Food-Drug Interaction
  - Absorption
  - Metabolism
  - Toxicity
  - Action
- Food-Herb Interactions

Therapeutic Index

Adverse Effects
- Side Effect
- Toxicity
- Allergic Reaction
- Idiosyncratic
- Iatrogenic
- Withdrawal Syndrome
- Carcinogenic
- Teratogenic
Medication Errors

- Any preventable event that may cause or lead to inappropriate medication use or harm
- 13 types of errors (see Table 7-3, pg 67)
- Causes of Medication Errors (90%)
  - Human factors
    - Performance deficits (30%)
    - Knowledge deficits (14%)
    - Miscalculation of doses (13%)
  - Communication Mistakes (15%) – handwriting, confusing abbreviations, decimals, apothecary vs. metric units
  - Name Confusion