Clinical Pharmacology 101

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Basic Pharmacology Review

Pharmacodynamic
Pharmacokinetic
Major Drug interactions (Top 10)
Opiate and NSAIDs
Antibiotics review
Major cardiovascular drugs
  Hypertension
  Lipid lowering agents
Drugs for ACS
  Thrombolytic
  Anti-platelets
  Anticoagulants
Endocrine Pharmacology
  DM, Thyroid, HRTs, GC
GI Pharmacology
  Acid related agents
  IBD, Nausea and constipation
  Hepatic diseases (HCV, HBV, ESLD and complications)
Mental Health Pharmacology
  Anti-depressants
  Anti- psychotics
  Anti-Anxiety
CNS and Neurology
  Antiepileptic Drugs
  Anesthetics
  Migraine Rx
Pulmonary
Hematology
Immune-modulating agents
Drugs:

- Chemical agents that interact with components of a biological system to alter the organism’s function. Examples of such components, sites of drug action, are enzymes, ion channels, neurotransmitter transport systems, nucleic acids and receptors. Many drugs act by mimicking or inhibiting the interactions of endogenous mediators with their receptors
Pharmacodynamics
Principles of Drug Action

- Effects of drugs determined by interaction with biological processes in the body

- Drug Action = [A] + [R] and [AR]
Basic principles

The first step of drug action on specific receptors is the formation of a reversible drug-receptor complex, the reactions being governed by the Law of Mass Action – rate of chemical reaction is proportional to the concentrations of reactants:

$$[R] + [A] \xrightarrow{k_{+1}} [RA] \xrightarrow{k_{-1}} E\text{FFECT}$$

modify factors

$R = \text{receptor}$

$A = \text{pharmakon (drug)}$

$RA = \text{drug-receptor complex}$

$k_{+1} = \text{association constant}$

$k_{-1} = \text{dissociation constant}$
Changes in Physiological Functions

paralysis    inhibition    -    +    stimulation    excitation

according to interactions with targets, effects of drugs are:

nonspecific
specific
PHARMACODYNAMICS

• At the cellular level: Most drugs exert their effects on the body by interacting with macromolecule “targets” which are usually on the surface or within cells.
Many drugs work by interacting with receptors, which can be divided into several groups:

- **intracellular receptors**
- **transmembrane enzymes**
- **receptors acting via G-protein**
- **ion channels**
- **other: enzymes (MAO) and transport mechanisms (Na+/K+ATPase)**
1. Membrane solubility allows lipid-soluble drugs to cross the cell membrane and bind to intracellular receptors.
2. Transmembrane proteins bind the drug at the extracellular side of the cell membrane and binding activates an intracellular enzyme site.
3. The transmembrane protein is linked to an enzyme via a G-protein.
4. The receptor is a transmembrane ion channel.
EXAMPLE OF A RECEPTOR STRUCTURE

Open

Inactivated

Na⁺

Na⁺

A

A

I

I

Na⁺

Carbamazepine
Phenytoin

Lamotrigine
Valproate

Na⁺
Receptors:

• **Regulatory proteins that interact with drugs or hormones and initiate a cellular response**
  – Ion channels
  – G-protein coupled receptors
  – Receptor-enzymes
  – Cytosolic-nuclear receptors

• **Act as transducer proteins**
  – Receptor-effector signal transduction
  – Post-receptor signal transduction provides for amplification of the signal
Classical Receptor Occupancy Theory

\[ \text{Stimulus} \rightarrow \text{Response} \]

K_a: Association rate constant
K_d: dissociation rate constant
L: Ligand (Drug)
R: Receptor
LR: Ligand-Receptor Complex

Stimulus: initial effect of drug on receptor
Properties of drugs

• **Affinity:** The chemical forces that cause the drug to associate with the receptor.

• **Efficacy:** The extent of functional change imparted to a receptor upon binding of a drug.
Properties of a biological system

• **Potency:** Dose of drug necessary to produce a specified effect.
  – Dependent upon receptor density, efficiency of the stimulus-response mechanism, affinity and efficacy.

• **Magnitude of effect:** Asymptotic maximal response
  – Solely dependent upon intrinsic efficacy.
  – Also called **efficacy.**
Full vs Partial agonists

• These terms are tissue dependent on
  – Receptor density
  – Cell signaling apparatus
  – Other receptors that are present
  – Drug history

• Partial agonists have both agonist and antagonist properties.
• **Partial agonists:** Drug that, no matter how high the dose, cannot produce a full response.

• **Inverse agonist:** Drug that binds to a receptor to produce an effect opposite that of an agonist. Stabilizes receptors in the inactive state.
Graded dose-response curves

• Individual responses to varying doses
• Concepts to remember:
  – **Threshold**: Dose that produces a just-noticeable effect.
  – **ED\(_{50}\)**: Dose that produces a 50% of maximum response.
Dose-response curve
Dose-response curve

Dose

Response

0
20
40
60
80
100
0.1 1 10 100 1000 10000
○ = Agonist
Dose-response curve

- **Ceiling**
- **ED50**
- **Threshold**
Full vs Partial agonists

The diagram illustrates the comparison between Full Agonist and Partial Agonist effects in terms of % Effect against Dose. The Full Agonist curve reaches 100% effect at lower doses compared to the Partial Agonist, which shows a more gradual increase in effect.
Inverse Agonist

![Graph showing the relationship between dose and percentage effect for different types of agonists. The graph distinguishes between Full agonist, Partial agonist, and Inverse agonist.]
Relative Potency

Effect vs. Dose graph showing the relative potency of substances A and B.
Relative Potency

Effect

Dose
Relative Efficacy
Antagonists

- **Competitive**: Antagonist binds to same site as agonist in a reversible manner.
- **Noncompetitive**: Antagonist binds to the same site as agonist irreversibly.
- **Allosteric**: Antagonist and agonist bind to different site on same receptor
- **Physiologic**: Two drugs have opposite effects through differing mechanisms
Competition

Effect

log [antagonist]

IC$_{50}$
Competitive antagonists

A B C

Dose

Response
Noncompetitive antagonists

![Graph showing dose-response curves for noncompetitive antagonists A, B, and C.](image-url)
Receptor regulation

• Reduced responsivity: Chronic use of an agonist can result in the receptor-effector system becoming less responsive
  – eg. alpha-adrenoceptor agents used as nasal decongestants
• Myasthenia gravis: decrease in number of functional acetylcholine nicotinic receptors at the neuromuscular junction.
Receptor regulation

- Increased responsivity: Chronic disuse of a receptor-effector system can result in an increased responsiveness upon re-exposure to an agonist.
  - Denervation supersensitivity at skeletal muscle acetylcholine nicotinic receptors
  - Thyroid induced upregulation of cardiac beta-adrenoceptors
  - Prolonged use of many antagonists (pharmacological as well as functional) can result in receptor upregulation
Receptor Upregulation

• Most receptors are internalized and degraded or recycled with age and use.
• Antagonists slow use-dependent internalization
• Inverse agonists stabilize the receptor in the inactive state to prevent internalization.
• The cell continues to produce receptors.
 Desired vs undesired effects: Indices of drug safety.

• Safety Index

• Therapeutic Index
Safety index: \( \text{LD}_1 / \text{ED}_{99} \)
First-Order Elimination

\[ C_t = C_0 e^{-kt} \]

- \( C_t \) is concentration after time \( t \)
- \( C_0 \) is the initial concentration (\( t=0 \))
- \( k \) is the elimination rate constant

- first-order logarithmic process
- that is, a **constant proportion** of the agent is eliminated **per unit time** (Birkett, 2002)

Half-Life Elimination (cont.)

• Repeated equal doses of a drug more frequently than 5 elimination half-times: result in drug being administered at a rate greater than its plasma clearance – accumulation in plasma.
For a zero order reaction A → products, rate = k:
For a first order reaction $A \rightarrow \text{products}$, rate $= k[A]$:

Length of half life is constant.
A drug was given intravenously at a dose of 200mg. The initial concentration in plasma (Co) was 10 µg/ml, and the Kel (elimination constant) was 0.02/h. Determine the plasma clearance (Clpl) and t1/2 for this drug.

Distribution volume: $V_d = \frac{\text{dose}}{C_0} = \frac{200 \text{ mg}}{10 \text{ mg/L}} = 20 \text{ L}$

$Cl_{pl} = V_d \times Kel = 20 \text{ L} \times 0.02/\text{h} = 0.4 \text{ L/h}$

$T1/2 = \frac{\ln 2}{Kel} = 0.693 \times 0.02 = 35 \text{ hours}$
Repeated Drug Dosing to Maintain SS Levels Within a Therapeutic Range

- Lower limit set by the drug level giving perhaps 50% of the maximum therapeutic effect.
- The upper limit is defined by toxicity NOT therapeutic effect and is the level causing toxicity in <5-10% patients.
Pharmacokinetics

• Defined: all aspects of drug distribution in the body after administration, ie. “what the body does to the drug”:
  • Absorption from administration site
  • Distribution into body compartments
  • Metabolism to active and inactive metabolites
  • Elimination of parent drug and metabolites

• Influences: concentration at site, response, toxicity
  • Influences: Pharmacodynamics: “what the drug does to the body”

• Changes in pharmacokinetics due strictly to renal failure usually not well defined.
Definitions

**Polypharmacy:** use of more than 5 medications
- inappropriate prescribing of duplicative medications where interactions are likely

**Adverse Drug Reaction (ADR):**
- drug interaction that results in an undesirable/unexpected event that requires a change in management
<table>
<thead>
<tr>
<th>DRUG</th>
<th>CATEGORY</th>
<th>REASON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>antihistamine</td>
<td>serious metabolic drug intxns</td>
</tr>
<tr>
<td>Bromfenac</td>
<td>analgesic</td>
<td>hepatotoxicity</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td></td>
<td>anorectic cardiovascular tox</td>
</tr>
<tr>
<td>Felbamate</td>
<td>anticonvulsant</td>
<td>aplastic anemia</td>
</tr>
<tr>
<td>Flosequinan</td>
<td>vasodilator</td>
<td>increased mortality</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>antibiotic</td>
<td>drug Intx/proarrhythmic</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>Ca channel blocker</td>
<td>serious drug intxns</td>
</tr>
<tr>
<td>Temafloxacin</td>
<td>antibiotic</td>
<td>drug Intx/severe ADR</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>antihistamine</td>
<td>serious drug intxn</td>
</tr>
<tr>
<td>Travefloxacin</td>
<td>antibiotic</td>
<td>hepatotoxicity</td>
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<tr>
<td>Cisapride</td>
<td>antihistamine</td>
<td>serious metabolic drug intxns</td>
</tr>
<tr>
<td>Baychol</td>
<td>Cholesterol</td>
<td>serious drug intx/renal failure</td>
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<tr>
<td>Vioxx</td>
<td>pain/NSAIDs</td>
<td>MI/CVD</td>
</tr>
<tr>
<td>Baxetra</td>
<td>pain/NSAIDs</td>
<td>skin Rx &amp; CVD</td>
</tr>
</tbody>
</table>
Drug Interactions:
“When the Holes Line Up”

Hansten PD, Horn JR. Modified from: James Reason, Human Error, 1990
Top Drug Interactions
Every NP needs to know

- Warfarin and NSAIDs
- Warfarin and TMP/SMZ
- ACE inhibitors — Potassium supplements
- ACE inhibitors and spironolactone
- Digoxin and Amiodarone
- Digoxin and Verapamil
- ACE-I and TMP/SMZ
- Warfarin and Cipro
- Thyroid and Iron
- SSRI plus tramadol
- HMG-CoA reductase inhibitor, gemfibrozil and erythromycin or itraconazole
**Clinically Significant Drug – St. John Wort Interactions**

<table>
<thead>
<tr>
<th>Object Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>serotonergic syndrome</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>↓ levels, transplant rejection</td>
</tr>
<tr>
<td>Digoxin</td>
<td>↓ digoxin levels</td>
</tr>
<tr>
<td>Estrogen</td>
<td>breakthrough bleeding</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↓ indinavir levels</td>
</tr>
<tr>
<td>Methadone</td>
<td>withdrawal sx’s</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↓ levels</td>
</tr>
<tr>
<td>Theophylline</td>
<td>↓ theophylline levels</td>
</tr>
<tr>
<td>Warfarin</td>
<td>↓ INR</td>
</tr>
</tbody>
</table>
Clinical coping

• Counteract “don’t ask-don’t tell”
  – Open and nonjudgmental discussion
  – Follow up herb use found in case histories
  – Explain importance of potential interactions

• Avoid SJW and warfarin interactions

• Patients on complicated medical regimens should avoid herbs and supplements unless carefully screened/supervised, but prioritize drugs with narrow therapeutic index, ie: carbamazepine, cyclosporine, digoxin, ethosuximide, levothyroxine, phenytoin, procainamide, theophylline, diltiazem, verapamil and warfarin
Pharmacokinetics

• Absorption: Not highly impacted by aging
• Variable changes in first pass metabolism due to variable decline in hepatic blood flow (elders may have less first pass effect than younger people, but extremely difficult to predict)
CLASSIFICATION OF MECHANISM

ALTERATIONS IN ABSORPTION

Complexation/Chelation

Example: antacids + tetracycline
Cipro and Iron
Iron and thyroid

Example: H-2 blockers + ketoconazole

Impact: dissolution of ketoconazole is decreased, resulting in reduced absorption
Pharmacokinetic Drug Interactions

• Common 3A4 Inhibitors
  – Grapefruit
  – Mandarin Orange
Pharmacokinetics-Distribution

- In elderly body fat ↑ 35%
- Lean body mass and total body water ↓ 20%
- Plasma volume ↓ 8-10%
- Highly lipophilic drugs widely distribute and are removed slowly
- Hydrophilic drugs toxic if loaded routinely
- ↓ Albumin leads to lower protein binding
Case

Patient with known epilepsy arrives in ER in status, gets 4 mg of ativan without breaking the seizure. Dilantin level is 6. Patient weighs 80 kg. How much Dilantin do you write for?

Bolus dose = $V_d (\text{desired conc} - \text{current conc}) \times \text{weight in kg}$

$= 0.7(20-6) \times 80 = 784\text{mg}$
Drug Distribution

• Hypoalbuminemia:
  – increase in unbound phenytoin concentrations in patients with hypoalbuminemia; measuring unbound phenytoin concentrations may be useful in these patients

• Renal impairment:
  – increase in unbound phenytoin concentrations in patients with renal disease; measuring unbound phenytoin concentrations may be useful in these patients
Case continued

You discover that the patient has HIV and that his last serum albumin was 2.2 gm/dl. Does this change how much you want to load?????? Assume same weight (80kg) and same dilantin level of 6.

Adjusted conc. = 12
First Pass Effect

- Pass through liver before reaching circulation
- Undergo metabolism by liver
Families of Cytochrome P450 Enzymes ("CYPs") are Based on Amino Acid Sequence Similarities
C. METABOLISM

1. Cytochrome P-450 isoenzymes

2. P-glycoprotein transport

3. Genetic polymorphism
   rapid acetylators
   extensive metabolizers (EM), poor metabolizers (PM)
CYTOCHROME P-450
Nomenclature

• 3-tier Classification (e.g. CYP 3A4)
  – family, subfamily, specific gene

• Lipid bilayer of ER -- hepatocytes, enterocytes
  – kidney, lung, and brain

• Oxidative Metabolism -- drugs, steroid hormones, prostaglandins

• Over 30 identified; CYP 3A4 metabolizes 50% of all prescribed drugs
  – CYP 3A4, CYP 2D6, CYP 1A2, CYP 2C (9/16)
Cytochrome P450

Cyt P450

ERY

FK-506
CYTOCHROME P-450
Considerations

• A. Substrate

• B. Inducers

• C. Inhibitors

Rate of drug elimination: rate of oxidation
# CYP3A4

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, FK506</td>
<td>Erythromycin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Clarithromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Diltiazem</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Felodipine, Isradipine</td>
<td>Ketoconazole</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Fluconazole</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>Itraconazole</td>
<td>Corticosteroids</td>
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<tr>
<td>Nitrendipine</td>
<td>Quinidine</td>
<td>Troglitazone</td>
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<tr>
<td>Digoxin, Quinidine</td>
<td>Grapefruit juice</td>
<td>St. John’s wort</td>
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<tr>
<td>Verapamil</td>
<td>Cimetidine</td>
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<tr>
<td>Warfarin</td>
<td>Indinavir</td>
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<td>Sildenafil</td>
<td>Fluoxetine</td>
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<td>Astemizole</td>
<td>Zileuton, Zafirlukast</td>
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<tr>
<td>Terfenadine</td>
<td>Verapamil</td>
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<tr>
<td>Pioglitazone</td>
<td>Amiodarone</td>
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# CYP 2D6

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<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
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<tbody>
<tr>
<td>Codeine</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
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<tr>
<td>Dextromethorphan</td>
<td>Fluoxetine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Labetalol</td>
<td>Phenobarbital</td>
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<tr>
<td>Paroxetine</td>
<td>Paroxetine</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Propafenone</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Quinidine</td>
<td></td>
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<tr>
<td>Risperidone</td>
<td>Sertraline</td>
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<tr>
<td>Timolol</td>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
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<tr>
<td>Nortriptyline</td>
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<td>Clozapine</td>
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<tr>
<td>Morphine</td>
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<td></td>
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<tr>
<td>Methadone</td>
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# CYP 2C

<table>
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<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Warfarin</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
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<td>Losartan</td>
<td>Cimetidine</td>
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<tr>
<td>Diazepam</td>
<td>Chloramphenicol</td>
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<tr>
<td>Imipramine</td>
<td>Fluconazole</td>
<td>Rifampin</td>
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<td>Amitriptyline</td>
<td>Isoniazid</td>
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<tr>
<td>Phenytoin</td>
<td>Ketoconazole</td>
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<tr>
<td>Rosiglitazone</td>
<td>Zafirlukast</td>
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<td>Fluoxetine</td>
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<td></td>
<td>Fluvoxamine</td>
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<td></td>
<td>Sertraline</td>
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<tr>
<td></td>
<td>Rosiglitazone</td>
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</table>
# CYP 1A2

<table>
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<tr>
<th>Substrate</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Cimetidine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clarithromycin</td>
<td>Phenobarbital</td>
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<tr>
<td>Diazepam</td>
<td>Erythromycin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Grapefruit juice</td>
<td>Smoking</td>
</tr>
<tr>
<td>Tacrine</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Ketoconazole</td>
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<tr>
<td>Zileuton</td>
<td>Quinolones</td>
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<tr>
<td>amitriptyline</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>imipramine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What Is Renal Insufficiency?

- Normal renal function: 90-150ml/min
- Decreased renal reserve: 60-90ml/min
- Mild renal insufficiency: 30-60ml/min
- Moderate renal insufficiency: 15-30ml/min
- Uremia/Severe renal failure: <15ml/min
Creatinine Clearance

Cockcroft-Gault formula:

\[
\text{CrCl}(\text{ml/min}) = \frac{(140 - \text{age[ysis]}) \times \text{weight[kg]}}{\text{SCr[mg/dL]}} \times 72
\]

For women: \( \text{CrCl} \times 0.85 \)
Creatinine Clearance

24 hour urine creatinine collection:

\[ \text{CrCl (ml/min)} = \frac{\text{urine collection (mg/dL)} \times \text{volume (ml)}}{\text{SCr (mg/dL)} \times \text{time (min)}} \]
Elimination

• Renal function may decline by 40-50% with age
  – Kidney mass decreases by 10-20% by age 80.
  – GFR decreases by 1ml/min/year from age 20-90.
    • decreased cortical perfusion rate and filtration pressure, atrophy, vascular lesions of small arteries, loss of glomeruli.
  – Renal plasma flow decreases by 1-2% per year from age 20-90.

• Decrease in renal blood flow exceeds the decrease in cardiac output.
  • compounded by various disease states, eg. CHF, hypotension.

• Tubular function decreases in proportion to GFR.
Why is the Kidney Vulnerable to Nephrotoxins?

- Patient Specific Factors
- Kidney Specific Factors
- Drug Specific Factors

Invariably some combination of these factors increases vulnerability!
Patient Specific Factors

• True or effective intravascular volume depletion
  - Prerenal azotemia
  - Sluggish urine flow

• Age (elderly)
• Sex (female)
• Race

• ARF or CKD
• Nephrotic syndrome
• Cirrhosis
• Obstructive jaundice

• Allergic response to certain medications
  - Immune response genes

• Metabolic perturbations
  - Electrolyte and acid-base disturbances
    - urine pH
    - urine crystal inhibitors

• Patient Specific Factors

- True or effective intravascular volume depletion
  - Prerenal azotemia
  - Sluggish urine flow
Kidney Specific Factors

- Altered pharmacogenetics
  - Renal transporters
    - loss of function mutations
    - altered regulation of the carrier (transport regulating kinases)
  - Cytochrome P450 enzyme gene polymorphisms
    - alter metabolism of drugs
Drug Factors

- ACE-I
- NSAIDs
- Antibiotics
  - AG, Vanco
  - Ceph, Pens
- Radiocontrast Dyes
- MTX
- PPI

- Acyclovir
- Newer HIV
- Allopurinol
- Antineoplastics
- Lithium
- Oral phosphate
- CSA, Tac, m-TOR
<table>
<thead>
<tr>
<th>Drug name</th>
<th>When to draw sample</th>
<th>Therapeutic range</th>
<th>How often to draw levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (Conventional dosing)</td>
<td>Trough: Immediately prior to dose</td>
<td>Gentamicin and Tobramycin:</td>
<td>Check peak and trough with 3rd dose</td>
</tr>
<tr>
<td>Gentamicin, Tobramycin,</td>
<td>Peak: 30 min after a 30-45 min infusion</td>
<td>Trough: 0.5–2 mg/L</td>
<td>For therapy less than 72 h, levels not necessary. Repeat drug levels weekly or if renal function changes</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td>Peak: 5–8 mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amikacin:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak: 20–30 mg/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trough: &lt; 10 mg/L</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides (24-h dosing)</td>
<td>Obtain random drug level 12 h after dose</td>
<td>0.5–3 mg/L</td>
<td>After initial dose. Repeat drug level in 1 week or if renal function changes</td>
</tr>
<tr>
<td>Gentamicin, Tobramycin,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Trough: Immediately prior to dosing 4–12 mcg/mL</td>
<td>Check 2–4 days after first dose or change in dose</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Trough: Immediately prior to dosing 150–400 ng/mL</td>
<td>Daily for first week, then weekly.</td>
<td></td>
</tr>
<tr>
<td>Drug name</td>
<td>When to draw sample</td>
<td>Therapeutic range</td>
<td>How often to draw levels</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 h after maintenance dose</td>
<td>0.8–2.0 ng/mL</td>
<td>5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients</td>
</tr>
<tr>
<td>Enoxaprin</td>
<td>4 hours after 2\textsuperscript{nd} or 3\textsuperscript{rd} dose.</td>
<td>0.7-1.1</td>
<td>Weekly and as needed</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>8 h after i.v. infusion started or changed</td>
<td>1–5 mcg/mL</td>
<td>As needed</td>
</tr>
<tr>
<td>Lithium</td>
<td>Trough: Before a.m. dose at least 12 h since last dose</td>
<td>Acute: 0.8–1.2 mmol/L</td>
<td>As needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic: 0.6–0.8 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Trough: Immediately prior to dosing</td>
<td>15–40 mcg/mL</td>
<td>Check 2 weeks after first dose or change in dose. Follow-up level in 1–2 months.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Trough: Immediately prior to dosing</td>
<td>10–20 mcg/mL</td>
<td>5–7 day after first dose or after change in dose</td>
</tr>
<tr>
<td>Free Phenytoin</td>
<td>Trough: Immediately prior to dosing</td>
<td>1–2 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>Drug name</td>
<td>When to draw sample</td>
<td>Therapeutic range</td>
<td>How often to draw levels</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Procainamide</td>
<td>Trough: Immediately prior to next dose or 12–18 h after starting or changing an infusion</td>
<td>Trough: 4 mcg/mL</td>
<td>As needed</td>
</tr>
<tr>
<td></td>
<td>Draw with procainamide sample</td>
<td>Peak: 8 mcg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–30 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>NAPA (n-acetyl procainamide) a procainamide metabolite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Trough: Immediately prior to 10–20 ng/dL next dose</td>
<td></td>
<td>weekly for first month then as needed</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Trough: Immediately prior to 5–10 ng/mL next dose</td>
<td></td>
<td>Daily for first week, then weekly.</td>
</tr>
<tr>
<td>Valproic acid (divalproex sodium)</td>
<td>Trough: Immediately prior to 40–100 mcg/mL next dose</td>
<td></td>
<td>Check 2–4 d after first dose or change in dose</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Trough: Immediately prior to dose</td>
<td>Trough: 10–20 mg/L</td>
<td>With 3rd dose (when initially starting therapy, or after each dosage adjustment). For therapy less than 72 h, levels not necessary. Repeat drug levels if renal function changes</td>
</tr>
<tr>
<td></td>
<td>Peak: 60 min after a 60 min infusion</td>
<td>Peak: 25–40 mg/L</td>
<td></td>
</tr>
</tbody>
</table>