Midterm review - February 26, 2004

**Pharmacokinetics:** (Walsh, Langer, et al.)

1. **Volume of distribution:**
   \[ V_d \text{ (in mLs or liters)} = \frac{D}{C_0} \]
   where \( D \) is drug dose (e.g. after bolus IV),
   \( C_0 \) = its plasma concentration at time 0

2. **First order Kinetics**
   \[
   \frac{dX}{dt} = -kX
   \]
   where \( k \) is the elimination rate constant and \( X(t) \) represents the amount of drug
   in the plasma as a function of time
   \[
   X(t) = X_0 e^{-kt} \Rightarrow C(t) = \frac{X_0}{V_d} e^{-kt}
   \]
   \[
   t_{1/2} = \ln 2/k = 0.693/k \quad \text{(note: } k \text{ has units of 1/time)}
   \]

3. **Clearance**
   \[ Cl = V_d \times k \]
   i.e. volume of plasma cleared of drug/unit time

4. **Constant (IV) infusion kinetics**
   Steady state is achieved when the infusion rate of a drug equals its rate of elimination:
   \[
   k_0 = (C_{ss} V_d) k \quad \text{where } C_{ss} \text{ is the steady state concentration}
   \]
   and \( k_0 \) is the rate of infusion
   \[
   C_{ss} = \frac{k_0}{(V_d k)} = \frac{k_0}{Cl} \Rightarrow \text{therefore Maintenance Dose (IV) } = C_{ss} Cl
   \]
   mathematically:
   \[
   \frac{dX}{dt} = k_0 - kX \Rightarrow X(t) = \frac{k_0}{k}(1-e^{-kt}) \quad \text{or } C(t) = C_{ss}(1-e^{-kt})
   \]
   The time needed to reach steady state concentration is strictly determined by the half life of
   elimination \( t_{1/2} \). To reach steady state more quickly, give a

   **Loading dose:** \( C_{ss} V_d \)
   which if given IV will instantaneously achieve steady state
   levels that can be maintained by IV infusion at a rate of \( k_0 \) (from above).

5. **Multiple dosing kinetics**
   You want to keep the concentration between \( C_{\text{max}} \) and \( C_{\text{min}} \) \Rightarrow
   Loading dose: \( C_{\text{max}} V_d \)
   Maintenance dose: \( (C_{\text{max}} - C_{\text{min}}) V_d \)
   Dosing interval (comes directly from first order equation):
   \[
   t = \frac{1}{k} \ln(C_{\text{max}}/C_{\text{min}})
   \]
   Maximal dose = \( V_D \times C_{\text{toxic}} \)  \quad \text{Maximal bolus dose given a certain toxic concentration}
   Minimum dose = \( V_D \times C_{\text{threshold of therapeutic effect}} \)
   If you know the target concentration, \( C_{\text{targets}} \) and want to maintain it at that target concentration, to
   calculate loading & maintenance dose:
   Loading target dose = \( C_{\text{target}} (V_d) \)
   Maintenance dose = \( C_{\text{target}}(Cl_T) \)
Renal Failure case: Toxicities limit maximal concentrations ($C_{\text{max}}$) of some drugs (digoxin, gentamicin). Requirements for minimum concentration ($C_{\text{min}}$) for biological activity mean you have to keep levels above a threshold (gentamicin). Renal clearance declines in renal failure, and for renally excreted drugs a patient could accumulate toxic levels. Basic strategies in renal failure patient are to decrease frequency of dosing (i.e. increase time interval between dosing) or decrease the dose, or both.

6. Bioavailability

Fraction of dose absorbed into systemic circulation is known as a drug’s bioavailability. AUC refers to the area under the plasma concentration vs. time curve:

$$AUC = \frac{F \times D}{C_l}$$

where $D$ is the dose, $F$ is the bioavailability (fraction absorbed), and $C_l$ is clearance

$F$ is usually measured by comparing AUC of a dosage form of drug given by one route divided by the AUC of the drug given IV (i.e. $AUC_{\text{oral}} : AUC_{\text{iv}}$)

Factors that influence bioavailability:

- First pass effects
- Chemical instability
- Nature of drug formation

7. Notes:

Lipophilic drugs tend to have large volumes of distribution which means they tend to exert their effects quickly and then redistribute into fat (ie propofol). As a consequence, they stick around and slowly leach out of the fat into the plasma. This may or may not be significant enough to cause lingering effects.

You can think of first order kinetics as the ability (e.g. of an enzyme) to increase its activity as a function of the concentration of the substrate. When the enzyme’s ability is maxed out (i.e. drug concentrations are too high), the enzyme operates at a fixed (maximum) rate known as the Zero order kinetics

A typical example of zero order kinetics is the metabolism of ethanol. (Also IV drips, aspirin metabolism, and phenytoin metabolism [mixed 0 and 1st order kinetics {Standaert lecture}] )

A drug could be completely absorbed, but if the rate of absorption is insignificant compared to clearance, its effect could be severely diminished

8. Langer Pharmacokinetics Lecture: Review briefly some of the problems in drug delivery, proposed solutions, and some of the important equations describing drug release from certain structures (i.e. zero order kinetics, release from a cylindrical reservoir). Always consider the side effect of a traumatic release of large quantity of the drug from the reservoir!!!
Receptors: (Strichartz, et al.)

1. Basic principle

\[
\begin{align*}
D & \leftrightarrow DR & \leftrightarrow DR^* (active) \\
potency/affinity & \uparrow \uparrow & \text{efficacy/coupling}
\end{align*}
\]

2. Efficacy

the maximum effect a drug can have – depends on the ratio \( DR^*/DR \) (which alone depends on reaction rates, i.e. efficacy depends on the specific drug for a single receptor)

3. Drug binding

\[
\text{fraction of receptor bounds by drug} = \frac{DR}{R_o} = \frac{D}{D + K_D}
\]

where \([D]\) is drug concentration, \(R_o = \text{concentration of total receptors} = \frac{R + DR}{R\text{ + DR}}\)

4. \(K_D\) (Dissociation constant = \(1/\text{affinity constant}\)): the concentration of drug at which half of the receptors are bound

5. \(EC_{50}\) (known also as \(K_{AP}\)): the concentration of drug needed to produce half maximal effect (see Katzung) – the apparent dissociation constant
   - not to be confused with \(ED_{50}\) – which is a dose that produces half-maximal effect or desired response in 50% of the recipients (see Katzung)

\[
\text{Effect / Max effect} = \frac{D}{D + K_{AP}}
\]

where \(D, R, DR\) are instantaneous concentrations of drug, free receptor, and bound receptor, respectively

6. Antagonism:

\text{Competitive (Surmountable)} \hspace{1cm} \text{Noncompetitive (Insurmountable)}

\[\text{Log Agonist (A)} \rightarrow \text{A} \rightarrow \text{A + agonist} \rightarrow \text{Response} \leftarrow \text{Log Agonist} \]

a. Competitive Antagonists:

The antagonist competes for binding at the receptor thus effectively increasing the \(EC_{50}\) (and \(K_D\))
Dose ratio equation:

\[
\frac{[D'] \text{ (with antagonist)}}{D} - 1 = \frac{A}{K_A}
\]

\[
EC_{50 \text{ with antag}} = EC_{50 \text{ without antag}} \times \left(1 + \frac{[A]}{K_A}\right)
\]

\[
\frac{EC_{50 \text{ with antag}}}{EC_{50 \text{ without antag}}} - 1 = \frac{[A]}{K_A}
\]

where \(D'\) = concentration of agonist D needed to produce the same effect in the presence of antagonist concentration A as D in the absence of antagonist.

b. Noncompetitive Antagonists:
Antagonist binds to a different site than the drug, eliminating the drug’s ability to bind receptor. So \(EC_{50}\) is unchanged, but the efficacy is reduced (except in the case of spare receptors – see below)

\[
V_{\text{max}} \text{ with inhibitor} = V_{\text{max}} \times (1 - y)
\]

where \(y = \text{occupancy by antag} = \frac{[A]}{([A] + K_A)}\)

c. Partial agonist/(antagonist)
A partial agonist has a lower efficacy than a full agonist. By competing for binding on a receptor, it decreases the effect of a full agonist as well as decreasing the effect of a full antagonist.

7. Spare receptors
Sometimes only a subset of the available receptors are needed to produce a full effect. The rest are spare receptors. Thus, in the presence of spare receptors, a noncompetitive antagonist may be ineffective until its concentration is high enough. Spare receptors increase sensitivity to drugs.

8. Different receptors
Different receptors would have different slopes on the dose-response curve & different \(EC_{50}\). If the mechanism were to be the same, you would see parallel curves. See Strichartz lecture.

9. Plots:
   a. Lineweaver-Burke → (Double reciprocal) plot:

   The plot of \(1/DR\) (or \(1/\text{response}\)) vs \(1/D\) = straight line
   \(1/R_0 = \text{max response}\)
   y-intercept is \(1/K_D\) or \(1/K_{Ap}\)
b. Scatchard: bound drug/free drug vs. bound drug:
   i. a change in slope represents a change in $K_d$ i.e. competitive antagonism
   ii. Equivalent slopes but different y-intercept implies a change in efficacy i.e. noncompetitive antagonism

\[
\frac{D_{\text{R}}}{D_{\text{D}}} (\text{bound/free drug})
\]

\[
= \frac{D_{\text{D}}}{D_{\text{D}} + \text{Antagonist}}
\]

\[
\text{Slope} = - \frac{1}{K_D}
\]

\[
\frac{D_{\text{R}} (\text{Bound drug})}{D_{\text{D}} (\text{D alone})}
\]

**Drug Metabolism: (Dershwitz)**

Drug metabolism is the body’s attempt to create a more polar product that is excretable in the urine. The liver is the workhorse in this process, though the kidney, the lung, the gut, and plasma enzymes also participate. Raising urinary pH ups excretion of acids, impairs excretion of bases. However, the extent of increasing drug excretion by raising/lowering the pH of urine depends on the pKa of the drug.

- Hepatic microsomal reactions (smooth ER):
  - Oxidative Reactions: **P450 enzyme system (Very important)**
    - Adds hydroxyl groups to compounds and requires NADPH produced by pentose phosphate shunt (clinically relevant) or Embden-Meyerhof pathway.
    - Glucuronidation: attachment of a molecule of glucuronic acid for further water solubility
  - Hepatic non-microsomal reactions (cytoplasm):
    - Esterases: ester hydrolysis
    - Monoamine oxidase: breaks down catecholamines as well as dietary amines (*tyramine* from cheese and wine) – also important in gut and brain. MAOI used in Parkinson’s and depression.
    - Alcohol and aldehyde dehydrogenase:
      - Ethanol $\rightarrow$ acetaldehyde $\rightarrow$ acetic acid

**Drug Activation:**

Sometimes metabolism leads to an active drug product or even toxic product:

- **Thiopental** (IV anesthetic) $\rightarrow$ pentobarbital (barbiturate)
- **Parathion** (insecticide) $\rightarrow$ paraoxon (cholinesterase inhibitor)
- **Carbon tetrachloride** (dry cleaning) $\rightarrow$ free radical scavenger
- **Terfenadine** (potentially toxic antihistamine precursor) $\rightarrow$ antihistamine

**Drug interaction:**

Enzyme **Inducers:**
Metabolic enzymes can be induced as a result of upregulation, decreased breakdown, etc. caused by the presence of a drug. This can lead to increased breakdown of other drugs, potentially making them ineffective.

P450 isoenzymes can be affected by (tiny subset):
- Cigarette smoke (polycyclic aromatic hydrocarbons)
- Phenobarbital (barbiturates)
- Rifampin (antibiotic, anti-TB that inhibit mRNA polymerase)
- Phenytoin (anti-epileptic)
- Carbamazepine (anti-epileptic, induces its own metabolism [Standaert lecture])

Enzyme Inhibitors:
In an entirely analogous fashion metabolic enzymes can be inhibited by the presence of a drug leading to potentially dangerous levels of other drugs being taken.
- Cimetidine and Ketoconazole (P450 inhibition)
- Disulfiram (aldehyde dehydrogenase) (metronidazole has a disulfuram like effect)

Plasma protein binding and displacement:
Drugs can bind to plasma proteins which may then serve as a reservoir. Potentially dangerous levels of drug maybe attained if a different drug displaces additional drug previously bound to protein – prototypical example is warfarin.

Pharmacogenetics: (Dershwitz, Case)

G6PD deficiency:
- Sex-linked: protective against malaria
- Red cells deficient in NADPH → glutathione peroxidase can’t be regenerated → oxidation leads to toxic H₂O₂ production normally broken down by glutathione peroxidase → hemolysis.

Drugs and compounds to be avoided:
- Primaquine (antimalarial)
- Nitrofurantoin (antimicrobial for UTI, etc)
- Naphthalene (moth balls)
- Fava beans

Pseudocholinesterase deficiency:
- Normally breaks down succinylcholine – when deficient post surgical paralysis can be prolonged.

Porphyria:
- Problem with heme synthesis
  - Barbiturates induce d-ALA synthetase which leads to accumulation of heme precursors (d-ALA) which are neurotoxic (King George III)

Acetyl transferase:
- Fast acetylators: autosomal dominant
- Slow acetylators: recessive
Potential toxicity from sulfonamides (component of sulfasalazine), isoniazid, hydralazine

Local Anesthetics: (Strichartz)
Anesthetics come in two basic chemical flavors. They are composed of an aromatic group linked to an amine by either an ester bond or an amide bond.

Esters: Procaine, Tetracaine, Benzocaine (topical), Cocaine (vasoconstrictor!)
Amides: Bupivicaine, Lidocaine, Mepivacaine, Etidocaine

(amide always have two “i”’s in their name; esters have only one)
The alkyl substituents on the amine can determine the hydrophobicity of the molecule. The different anesthetics differ mainly in pharmacokinetics – these differences were not the focus of interest.

The most important thing to know about local anesthetics is how they work. They bind to and block Na channels – but from the inside of the cell membrane. In particular, they bind preferentially to inactive and open channels which predominate in depolarized states. Neurons which are firing rapidly as well as neurons persisting in a depolarized state are making inactivated and active channels more available to bind the anesthetic. As a result they are “selectively” blocked – this called use-dependent blockade. This is important in two settings: cardiac arrhythmias and pain. Pain fibers fire more rapidly than motor neurons and so are selectively blocked. In the heart, abnormal automaticity and ischemic tissue both promote use-dependent blockade by lidocaine.

Anti-Arrhythmic Drugs: (Ruskin)
Key points to know are the classes and mechanism of action of drugs in each class (i.e. I-IV). Basic idea: class I blocks Na channel, class II is beta blocker, class III is K channel blocker (+other function), class IV is calcium channel blocker. Know also the mechanism of different types of arrhythmia (i.e. reentry arrhythmia, torsade de pointes, etc) & methods to block it.

<table>
<thead>
<tr>
<th>Class</th>
<th>Action</th>
<th>Representative Drugs</th>
<th>Some Uses (Drugs of Choice)</th>
<th>Some Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Block open/inactive Na channels (use dependent blockade)</td>
<td>&lt;see below, IA, IB, IC&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>Prolong repolarization (“moderate” Na channel block, may also block K)</td>
<td>Quinidine, procainamide, disopyramide</td>
<td>AFib, ventricular arrhythmia</td>
<td>Torsades de pointes; Quinidine: cinchonism, hypersensitivity, thrombocytopenia; Procainamide: lupus</td>
</tr>
<tr>
<td>IB</td>
<td>Shorten repolarization (“weak” blockers of Na channel)</td>
<td>Lidocaine, mexiletine, tocainide, phenytoin</td>
<td>Sustained Ventricular tachycardia, VFib</td>
<td>Generally low toxicity: some CNS effects</td>
</tr>
<tr>
<td>IC</td>
<td>Little effect on repolarization (“strong” blocker of Na channel)</td>
<td>Encainide, flecainide, propafenone</td>
<td>AV reentry, WPW</td>
<td>CAST trial found increased mortality 2-3 fold over placebo.</td>
</tr>
<tr>
<td>II</td>
<td>Beta-Adrenergic Blockade</td>
<td>Propanolol, esmolol, acebutolol, l-sotalol</td>
<td>tachyarrhythmias caused by increased sympathetic activity, AFib, Atrial flutter</td>
<td>Bradycardia, LV block, depress LV function</td>
</tr>
</tbody>
</table>
### III

**Prolong Repolarization (Potassium Channel Blockade; Other)** [no effect on phase 0, but lengthen effective refractory period]
- Ibutilide, dofetilide, sotalol (d,l), amiodarone, bretylium
- Atrial fibrillation/flutter
- Ventricular arrhythmias
- Sinus bradycardia; QT elongation → delayed after depolarizations → torsade de pointes. Amiodarone: thyroid dysfunction, pulmonary fibrosis, photosensitivity & blue skin, hepatotoxic

**Calcium Channel Blocker** (decrease rate of phase 2 depolarization, slow conductance in tissues like AV node)
- Verapamil, diltiazem, bepridil
- Atrial Fibrillation, Atrial Flutter, SVT, atrial node reentry, atrial automaticity
- Sinus bradycardia, AV block, negative inotropy

### IV

**Miscellaneous Actions**
- Adenosine: SVT, AV node reentry
  - Hypotension, metallic taste, dyspnea
- Digoxin: Prolong effective refractory period, decrease conduction velocity
  - Anorexia, abdominal pain, nausea, vomiting, diarrhea, headache, confusion, abnormal vision (yellowish vision)
- Magnesium: Torsades de pointes

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**Autonomic Pharmacology: (Rosow)** [huge chapter!]

As long as you remember the sympathetic/parasympathetic system, the autonomic drugs are quite straightforward. When a drug is nonselective, its side effects are the other autonomic effects not mentioned in the therapeutic use. The following list only main usages – there may be others.

**Adrenergics** (primary neurotransmitter – NE)
- $\alpha_1$ mediates vasoconstriction, mydriasis, increased tone in bladder sphincter
- $\alpha_2$ mediates presynaptic inhibition of norepinephrine release
- $\beta_1$ mediates increased chronotropic, inotropic effects on heart as well as increased lipolysis in fat
- $\beta_2$ mediates vasodilation, bronchodilation, increased muscle and liver glycogenolysis, relaxes uterine smooth muscle

**Cholinergics** (only neurotransmitter – Ach)
- Muscarinic receptors (we consider) are found at parasympathetic effector sites.
- Nicotinic receptors are found at the neuromuscular junction and at autonomic ganglia.

**Adrenergic Drugs:**

**Presynaptic:**

**Adrenergic Blocking**
- $\alpha$-methyl-p-tyrosine: inhibits tyrosine hydroxylase, blocking the synthesis of norepinephrine.
α-methyldopa: undergoes transformation to become α-methyl-NE and α-methyldopamine. Effective agonist at post-synaptic adrenoceptors. Also an alpha 2-receptor agonist.

Reserpine: blocks incorporation of NE into vesicles
Therapeutic use: potential use in hypertension – results in gradual decline in blood pressure, ↓ heart rate

Guanethidine: blocks release of NE containing vesicles into nerve terminal
Therapeutic use: potential use in hypertension, but not commonly used anymore
Adverse effects: excessive sympathetoplegia can interfere with male sexual function, cause orthostatic hypotension, etc.

Bretylium: blocks release of NE containing vesicles into nerve terminal
Therapeutic use: used as an antiarrhythmic

Adrenergic Potentiation
Pargyline: blocks monoamine oxidase (MAO) which breaks down NE in cytoplasm – leads to “overstuffed” vesicles; also breaks down tyramine and other food stuff amines in the gut
Therapeutic use: used commonly for its CNS effects – in Parkinson’s disease and depression

Entacapone: nitro-catechol compound that inhibits catechol-O-methyltransferase (COMT); used in treatment of Parkinson’s

Cocaine (Case)
- blocks reuptake of catecholamines (NE, DA) – leads to excess stimulation of receptors by lingering catecholamines in the synapse
- Cocaine has structure of ester local anesthetic (and is used as local topical anesthetic for eye).
- Cocaine has stimulatory effects on CNS and cardiovascular system by blocking catecholamine reuptake.
  - Euphoria, addiction, tolerance
  - HTN, coronary vasospasm → MI

Imipramine: same mechanism as cocaine
Therapeutic use: One of the first tricyclic antidepressants (TCA)

Postsynaptic Adrenergic Agonists
α1, α2, β1, β2:
Epinephrine: natural catecholamine that can activate all adrenergic receptor types, released primarily by adrenal medulla
Therapeutic uses: bronchospasm, anaphylactic shock, anesthetics, glaucoma

Norepinephrine: natural catecholamine released at most adreneric synapses – has weak β2 effect
  Therapeutic use: sometimes used as a pressor in shock (Dopamine is better – see below)

Dopamine: natural catecholamine with actions in the basal ganglia as well as at α (at high conc) and β (at low conc) adrenergic receptors; in the kidney distinct dopamine receptors D1,D2 cause vasodilatation of renal and mesenteric vasculature upon activation
  Therapeutic use: drug of choice for shock – raises blood pressure by stimulating β1 and avoids kidney shutdown through the presence of D1,D2

α1, α2:
  Phenylephrine (more α1): synthetic direct acting α agonist
    Therapeutic use: nasal decongestant, raise blood pressure

α1:
  Methoxamine: synthetic agonist selective for α1
    Therapeutic use: used to overcome hypotension with certain anesthetics, also used in supravent tachycard

α2:
  Clonidine: synthetic agonist selective for α2
    Therapeutic use: used in essential hypertension to lower blood pressure by acting at CNS vasomotor centers

β1, β2:
  Isoproterenol: non-selective synthetic agonist
    Therapeutic use: rarely used as a bronchodilator in asthma

β1:
  Dobutamine: synthetic catecholamine with β1 selectivity
    Therapeutic use: increase cardiac output in CHF; does not increase heart rate significantly, placing little additional oxygen demand on the heart

β2:
  Terbutaline + Albuterol: both synthetic β2 agonists with similar properties
    Therapeutic use: commonly used in asthma as a bronchodilator; terbutaline also used to reduce uterine contractions in premature labor (ritodrine is more commonly used now)
Antagonists

$\alpha_1, \alpha_2$ mixed:
Phenoxybenzamine: non-selectively links covalently to $\alpha_1, \alpha_2$ receptors; cells must synthesize new receptors

**Therapeutic use:** used in treatment of pheochromocytoma

Phentolamine: reversible non-selective antagonist

**Therapeutic use:** potential use in diagnosis of pheochromocytoma

$\alpha_1$ selective:
Prazosin: selective competitive antagonist at $\alpha_1$ receptors

**Therapeutic use:** used to decrease blood pressure, also to promote urinary sphincter relaxation in patients who have BPH and difficulty urinating (can also use a muscarinic agonist)

**Pheochromocytoma case:**
- Catecholamine-producing tumors that originate from chromaffin cells of the adrenergic system; secrete both norepinephrine and epinephrine
- Sx: HTN (poor response to conventional treatment), paroxysmal symptoms suggestive of seizure disorder/anxiety attacks
- Dx: urinary and plasma metabolites (Review degradation of catecholamines via COMT and MAO)
- Tx: laparoscopic partial adrenalectomy, $\alpha$-adrenoceptor antagonists such as phenoxybenzamine, phentolamine, and prazosin to control the hypertension, $\alpha$-adrenoceptor blockade in severe cases (after beta blockade)

$\beta_1, \beta_2$:
Propanolol: non selective $\beta$ blocker

**Therapeutic uses:** hypertension, glaucoma, hyperthyroidism, Angina, protection against MI

**Adverse effects:** obvious – but listed here anyway: bronchoconstriction, arrhythmias, glucose metabolism disturbances

Pindolol: partial agonist (see section on receptors) at $\beta_1$ and $\beta_2$

**Therapeutic use:** effective at treating hypertensives who have bradycardia – further decrease in heart rate is less pronounced

$\beta_1$ selective:
Metoprolol, Atenolol are selective B1 blockers

**Therapeutic uses:** useful in hypertensive patients with impaired pulmonary function, diabetic hypertensives receiving insulin or other oral hypoglycemics
**Indirect Acting Agonists of Adrenergic System:**

Amphetamine: causes release of vesicles from presynaptic adrenergic terminal

*Therapeutic use:* potential use in depression, narcolepsy, appetite control

Ephedrine: causes release of vesicles (as above) as well as acting directly on β and α receptors

*Therapeutic use:* has been used for asthma, blood pressure elevation, and as a nasal decongestant (less common now)

**MAO Inhibitors (MAOI)**

- Endogenous adrenoreceptor agonists (NE, E, Dopamine) are rapidly metabolized by COMT (catechol-O-methyltransferase) and MAO (monoamine oxidase).
- MAOI increases the stores of catecholamines in storage vesicles and may potentiate the action of indirect-acting sympathomimetics.
- Some MAOIs: isocarboxazid, pargyline, tranylcypromine (selegiline is for Parkinson’s)
- Tyramine: same mechanism as ephedrine (causing release of catecholamines from vesicles); comes from fermented cheese and Chianti wine; normally degraded by gut monoamine oxidase (MAO)
  - *Adverse effects:* In someone on MAOI (e.g. for atypical depression), tyramine build up can cause a hypertensive crisis
- MAOI are of interest in hypertension also because they also cause the formation of the *false transmitter* octopamine. A *false transmitter* is a substance that is stored in vesicles and released into synaptic cleft but lacking the effect of a true transmitter. Octopamine is generated in sympathetic postganglionic neuron terminals and stored in vesicles along with small amount of NE. Normal nerve action potentials release this weak false transmitter with NE, resulting in diminished vascular and cardiac responses. This along with possible effects of tyramine (hypertensive crisis) means MAOI should not be used in hypertension.

**Cholinergic Drugs:** (Rosow, Strichartz, AChE case)

**Presynaptic**

Hemicholinium: blocks uptake of choline, the precursor of acetylcholine, thus depleting cholinergic terminals of transmitter

Vesamicol: blocks vesicular uptake of acetylcholine in presynaptic terminal

botulinum-toxin: blocks release of Ach vesicles in to synapse

alpha-latrotoxin: black widow toxin that oligomerizes to form membrane pores and stimulates large release of neurotransmitters

**Postsynaptic**

**Nicotinic Agonists**

Acetylcholine: endogenous neurotransmitter that is a *quaternary amine*; can not be given as a drug due to its breakdown in the plasma by an esterase as well as the challenge of reaching synapses in high enough concentration; a
Nicotine: classic nicotinic agonist; no therapeutic use

**Nicotinic Antagonists**

Succinylcholine: Ach analog resistant to breakdown by acetylcholinesterase (AChE); produces extended depolarization at neuromuscular junctions which results in paralysis – initial effect of depolarization is muscle contraction, fasciculations; *depolarizing muscle relaxant* no fade is observed. 
*Therapeutic use:* used as a FAST onset muscle relaxant in surgery  
(remember pseudocholinesterase deficiency - rare)

Pancuronium: *non-depolarizing muscle relaxant binds to nicotinic receptor at NMJ* without activating – behaves as a competitive antagonist; induces paralysis; 
*Therapeutic use:* also used as a muscle relaxant in surgery – avoids the fasciculations of succinylcholine which can cause muscle soreness, but is not as fast

cis-atracurium: non-depolarizing muscle relaxant; chance of causing *histamine release*

d-tubocurarine: same actions and use as pancuronium

α-bungarotoxin: also a nondepolarizing nicotinic blocker – found in snake venom; not used in anesthesia

**Ganglionic Nicotinic Antagonists**

Hexamethonium + Trimethaphan: selectively block nicotinic receptors at autonomic ganglia
*Therapeutic use:* Trimethaphan is currently only used for the initial control of blood pressure with acute dissecting aortic aneurysm – it reduces blood pressure and prevents sympathetic reflexes, reducing the rise of pressure rise near the tear

**Muscarinic Agonists** (look at powerpoint slide from AChE case)

Muscarine: classic compound found in certain mushrooms (has activity at nicotinic receptors as well)

Methacholine: analog of Ach, less susceptible to AChE

Carbachol: analog of Ach resistant to AChE (also has nicotinic action) 
*Therapeutic use:* sometimes applied to eye to cause pupillary contraction, relieving intraocular pressure

Pilocarpine: alkaloid analog of Ach, also stable against AChE
*Therapeutic use:* Drug of Choice in emergency reduction of intraocular pressure in both kinds of glaucoma
**Muscarinic Antagonists**

Atropine: a “belladonna” alkaloid, competitive inhibitor at muscarinic Receptors; at high concentrations it can enter the CNS

*Therapeutic uses:* Antidote for cholinergic agonists from above as well as AChE inhibitors (see below), antisecretory drug used to block pulmonary secretions

*Cosmetic uses:* makes eyes pretty – “belladonna”

Scopolamine: also a “belladonna” alkaloid, similar to atropine but enters CNS much more readily

*Therapeutic use:* used primarily in motion sickness (more effective as a preventive measure)

**Acetylcholinesterase Inhibitors** (look at powerpoint from AChE case)

Physostigmine: when AChE attempts to hydrolyze this alkaloid it gets trapped in a (carbamoyl) intermediate that has a long half life; Ach can exert its effects at postsynaptic receptors for a longer period of time; enters CNS

*Therapeutic use:* potentiating certain parasympathetic effects – increases intestinal and bladder motility, sometimes used in glaucoma to cause miosis which relieves pressure

Neostigmine: same mechanism as physostigmine, but is more polar so it does not cross BBB; it also has more effect at NMJ

*Therapeutic use:* sometimes used in symptomatic treatment of Myasthenia gravis

Parathion + Malathion: organophosphate compounds used in insecticides; They trap AChE in a phosphorylated intermediate which on its own never recovers – therefore these compounds are toxic

Soman: nerve gas; even more potent organophosphate – deadly, but organophosphate antidotes exist, namely, atropine and pralidoxime (see below)

Echothiophate: a less potent organophosphate used clinically

*Therapeutic use:* prolonged relief of pressure in glaucoma (1 week)

Pralidoxime (2-PAM): regenerates AChE after phosphorylation; must be applied before the phosphorylated AChE “ages” i.e. undergoes a dealkylation reaction that makes it extremely stable

*Therapeutic use:* organophosphate poisoning antidote
Anti-hypertensives: (DiSalvo, Rosow)

Drugs (and their classes) that Affect the Renin-Angiotensin System

- Hydrochlorothiazide: Thiazide Diuretic
- Furosemide: Loop Diuretics
- Spironolactone: Aldosterone antagonist
- Enalipril, Captopril, Lisinopril: ACE inhibitors
- Losartan: Angiotensin II receptor antagonist (ARB)

The newest studies have shown that diuretics provide virtually equal efficacy as many of the newer, fancier drugs like ACE Inhibitors and ARBs.

Sympathetic Nervous System

- **β blockers**
  - Mixed α,β blockers = Carvedilol, Labetalol

  Provide non-selective β-blockage (minimal β2-agonist activity) with α1-blocking activity, causing both reduction in heart rate and peripheral vascular resistance. CO declines less than with β-blockers alone

Direct Acting Vasodilators

Induce vascular smooth muscle relaxation by a different mechanism than sympathetics. Not typically used as first line therapy – almost always in combination with a β blocker and a diuretic as a result of the reflexes that vascular relaxation would induce.

- Hydralazine: may cause lupus like effects
- Nitroglycerin: must be metabolized to NO. Reduces preload more than reduces afterload.
- Nitroprusside – used in hypertensive crisis. Must be delivered IV as a result of a short half-life
(minutes). Its metabolism results in cyanide production though rarely in dangerous quantities – overdose can be treated with thiocyanate (see case below).

**Ca channel blockers** (diltiazem, nifedipine, etc)

Block Ca entry into smooth muscle and cardiac muscle needed for contraction. Often they have intrinsic natriuretic activity. Thus they could in principle be given as monotherapy if diuretics and β blockers are contraindicated or ineffective.

**Congestive Heart Failure: (DiSalvo)**

Recognize how therapy has changed over time. Only 10-15 years ago it was thought to use inotropic agents to boost the cardiac output of the failing heart (dobutamine, digoxin). Now, therapy seeks to use beta antagonists to lower strain on the heart. Recall the major graph from DiSalvo’s presentation that describes the drugs which lower mortality (*and note all block peripheral and myocardial neurohumoral activation*).

- **ACE inhibitors** show benefit across NYHA I to IV
- Add **beta blocker** in NYHA II to IV patients (remember carvedilol, mixed alpha and beta blocker, which was shown to decrease mortality in HF. However, large study of metoprolol, a selective beta 1 vs. carvedilol will be completed this year)
- Finally add **spironolactone** in NYHA III and IV patients.

Other drugs that may provide symptomatic benefits include diuretics, digoxin, etc. Proof of mortality reduction?

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**Nitric Oxide: (Zapol)**

- **NO** is a free radical molecule produced by endothelial nitric oxide synthase from Arginine in endothelial cells; it moves to smooth muscle cells and binds guanylate cyclase via a heme group. cGMP is produced, and it helps to relax SMC.
- NO is rapidly bound by heme in the blood. NO given via inhalation thus acts only locally and does not exert any systemic effect. There is little methemoglobinemia.
  - Thus inhaled NO is a pulmonary vasodilator
  - NO can lower pulmonary pressures and improve PaO2
- **ARDS:** preferentially dilates vessels of well-ventilated alveoli (“steal” phenomenon), thus improving a V/Q mismatch
- Persistent pulmonary hypertension: lowers pulmonary pressures (may blunt adverse pulmonary vascular remodeling)
- Note that nitrovasodilators used in cardiology (nitroglycerin, isosorbide dinitrate, sodium nitroprusside) all release nitric oxide via enzymatic metabolism. NO released from these compounds acts on vascular smooth muscle (many are relative venodilators which reduce preload).
**Immunopharmacology (Transplant Immunosuppression):**

- **Goal of therapy** is to limit acute/chronic rejection while minimizing side effects
- **Several available agents** to inhibit various parts of APC-T cell activation
  - **Steroids** (e.g. Prednisone): block NF-AT signaling which lowers IL-1,6 production. Systemic, broad spectrum, non-specific effects on leukocytes. Side effects: Cushingoid syndrome
  - **Cyclosporine**: complex with cyclophilin and block calcineurin. IL-2 production and T-cell activation blocked. Toxicity: 3N’s and 7H’s
  - **Tacrolimus**: bind FK506 and also block calcineurin (similar to cyclosporine)
  - **Cell Cycle Inhibitors**: block nucleotide synthesis, preventing completion of S phase. Examples are azathioprine (purine anti-metabolite), MMF (prevents recycling of guanosine nucleotides), leflunomide (prevents de novo pyrimidine synthesis), cyclophosphamide (alkylating agent=DNA damage; side effect is hemorrhagic cystitis)
  - **OKT3**: murine anti-TCR/CD3 mAb
  - **Sirolimus**: inhibits IL-2 mediated signaling, blocks G1→S transition, inhibit T and B cell activation
    - Now coated stents with sirolimus
  - **Newer agents**: **Three major TNF blockers**: etanercept (sTNFR), infliximab (chimeric IgG1 that binds TNF), anakinra (antagonize IL-1R)
- **Relationship of immunosuppression and chemotherapy:**
  - cancer cells proliferate constantly while immune cells proliferate in burst in response to stimuli (so you can time when you need immunosuppression),
  - immunosuppression given in continuous low dose vs. cancer in high dose pulses (to allow normal proliferation of normal cells between doses)
  - For immunosuppression, can target clones that are rapidly dividing because of exposure to specific antigen. In chemotherapy, not much selective difference from normal cells, and target cancer cells through inherently higher growth rate.
### Lipid Lowering Drugs (Lees):

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect on LDL</th>
<th>Effect on HDL</th>
<th>Effect on TG</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Acid Resins</td>
<td>Cholestyramine, Colestipol</td>
<td>Inhibit enterohepatic cycle; more bile excreted so more cholesterol converted into bile</td>
<td>↓↓</td>
<td>-</td>
<td>slight</td>
<td>Compliance: bad taste, severe GI discomfort</td>
</tr>
<tr>
<td>Niacin</td>
<td>Niacin</td>
<td>Inhibit lipolysis, lower LDL and VLDL, raise HDL</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
<td>Red flushed and itchy face / dermatitis (compliance)</td>
</tr>
<tr>
<td>Lipoprotein Lipase Inhibitors</td>
<td>Fenofibrate Gemfibrozil</td>
<td>Stimulate lipoprotein lipase. May also upregulate PPARs?</td>
<td>↓</td>
<td>↑</td>
<td>↓↓↓</td>
<td>Myositis, liver effects (increased liver enzymes)</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitor</td>
<td>Statins = lovatstatin, pravastatin etc.</td>
<td>Inhibit HMG-CoA reductase, rate determining step of endogenous cholesterol synthesis</td>
<td>↓↓↓</td>
<td>↑</td>
<td>↓</td>
<td>Myositis, increased liver enzymes</td>
</tr>
<tr>
<td>Sitostanol</td>
<td></td>
<td>Inhibit dietary cholesterol absorption</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Diagram:**

1. **Cholestyramine**
   - A bile acid-binding resin that, by ↑ excretion of bile acids, diverts endogenous cholesterol to bile acid production and thereby ↓ LDL.
   - INTESTINES
   - Bile acids (95%)
   - Chylomicrons
   - Chylomicron remnants
   - Lipoprotein lipase
   - VLDL
   - LDL
   - HDL
   - LCAT
   - EXTRAHEPATIC TISSUES
   - Pravastatin
   - Simvastatin
   - Lovastatin
   - Inhibition of HMG-CoA reductase inhibits endogenous cholesterol production, causing upregulation of LDL and IDL receptors and thereby ↓ serum levels of these two lipoproteins.

2. **Gemfibrozil**
   - A fibric acid derivative that ↑ lipoprotein lipase activity, thereby promoting catabolism of VLDL; also may inhibit hepatic secretion of VLDL.
Movement Disorders (Standaert):
Parkinson’s Disease involves loss of dopaminergic neurons in substantia nigra. Chief symptoms are rigidity, bradykinesia, and tremor. There are also many other classic symptoms.

Pharmacologic treatment of Parkinson’s involves methods to increase CNS dopamine.

1. Restore dopamine levels in CNS: Levodopa (L-DOPA) is used because dopamine does not cross BBB. L-DOPA is converted to dopamine by DOPA decarboxylase in CNS.
   a. Recall how tolerance develops. Requires either elaborate dosing schemes or drug holidays (not very successful).

2. Helping to maintain levels of levodopa:
   a. Carbidopa: inhibits peripheral decarboxylation of DOPA
      i. Combination of levodopa/carbidopa = Sinemet
   b. Entacapone: inhibits catechol O-methyltransferase (increase t1/2)
   c. Selegiline: inhibits central MAO-B (vs. other MAOI which inhibit MAOA)

3. Dopamine agonists / mimetics: Bromocriptine, Pergolide
   a. Trihexyphenidyl: anti-muscarinic side effects
   b. Amantadine: also anti-viral, has anti-cholinergic effects

Anti-psychotics: all antagonize dopamine receptors for psychotic illnesses and schizophrenia. As dopamine blockers, can cause Parkinsonian-like side extrapyramidal effects (dystonia, akathisia, choreoathetosis). Two major side effects: tardive dyskinesia (choreiform disorder affecting mouth and face which persists after treatment stopped [lip smacking]) and neuroleptic malignant syndrome (muscle rigidity, hyperthermia, increased creatinine kinase; treat with dantrolene, cool patient).
Typical anti-psychotics: block D<sub>2</sub> receptors but also have significant anti-cholinergic effects. These three listed in increasing order of D<sub>2</sub> blockade and decreasing order of anti-cholinergic effect.

- Chlorpromazine, Thioridazine, Haloperidol

Atypical anti-psychotics: primarily blocks D<sub>4</sub> receptors (and some other subtypes D<sub>2</sub>)

- Clozapine: causes agranulocytosis and requires regular blood checks
- Risperdal, olazepapine, quietapine, zisprasidone, aripiprazole, etc.

**Depression (Standaert):**

Depression Pharmacotherapy: based on amine hypothesis ➔ increase levels of dopamine, norepinephrine, serotonin

- Tricyclics and heterocyclics: block reuptake of serotonin and norepinephrine. Have anti-cholinergic side effects
  - Amitriptyline, nortripyline, trazodone (sedation and priapism)
- SSRIs: less anticholinergic side effects, but can inhibit P450 (especially fluoxetine)
  - Fluoxetine, sertraline, citalopram, escitalopram, paroxetine
- Non-selective MAOI: used for atypical depression (hyperphagia, hypersomnolence)
- Bupropion: structurally similar to tricyclics, but may actually help release norepinephrine. Also used in smoking cessation (Zyban v. Wellbutrin branding)

**Anxiolytics/Anticonvulsants (Standaert):**

**Sedative / Hypnotics:**

- Two major classes: benzodiazepines and barbiturates
- Both bind to GABA<sub>A</sub> receptor (which regulates inhibitory transmitter GABA).
  - Benzodiazepines increase frequency of channel opening.
  - Barbiturates prolong duration of opening.
- Benzodiazepines
  - Used as anti-anxiety and for sedation (also anesthesia)
  - Differentiated based on half lives:
Short: *midazolam*, triazolam
Medium: temazepam, lorazepam
Long: *diazepam*, flurazepam
Benzodiazepine antagonist: *Flumazenil*

- **Barbiturates**
  - Major toxicities are sedation and respiratory depression.
  - Only “treatment” for barbiturates is to give sodium bicarbonate and force urinary excretion via alkalinization (and give respiratory support until effects wear off)

- **Tolerance and cross tolerance**
  - Chronic use of either class results in tolerance to all members of that class and cross-tolerance to other class.
  - Both produce dependence; withdrawal may create anxiety, agitation, seizures.

**Anti-convulsants (Standaert):**
Some mechanisms include blocking sodium channel conductance and increasing GABA channel conductance. Know basic mechanisms and members of each class.

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**Na Channel blockers: phenytoin, fosphenytoin, and carbamazepine**


*Fosphenytoin:* water soluble prodrug metabolized to phenytoin in blood. Note Dr. Standaert compared the price of phenytoin and fosphenytoin for 1200 mg, about $1.00 vs. $119, but he said MGH uses almost all fosphenytoin because you can avoid using the propylene glycol vehicle and its side effects, which probably pays for the higher cost of fosphenytoin

*Carbamazepine:* used for partial and tonic-clonic seizures. Side effects include agranulocytosis and P450 induction.

Barbiturates: *Phenobarbital* and *Primidone:* used for tonic clonic seizures
Benzodiazepines: *Diazepam, Lorazepam:* used for status epilepticus

*Valproic acid* and *Ethosuccimide:* for absence seizures. Side effects include birth defects / spina bifida and GI distress respectively.
**Miscellaneous Case Presentations:**

**MGH OR Exercises: (Rosow)**
- **Propofol:** highly lipophilic alkylphenol agent (must be given in propylene glycol vehicle as opposed to water; high lipophilicity distributes propofol into CNS readily); used as sedative hypnotic and rapid induction of anesthesia
- **Isoflurane:** halogenated inhaled anesthetic for induction or maintenance of anesthesia; relatively non-toxic
  - Compare to halothane (hepatotoxicity) and methoxyflurane (renal toxicity = interstitial nephritis) and enflurane (seizures)
- **Thiopental:** barbiturate used for rapid induction of anesthesia

**Warfarin Case**
- Warfarin: blocks the regeneration of Vitamin K; since Vit K is needed to activate clotting factors II,VII,IX,X, anticoagulation results;
- Warfarin’s action takes time both to take effect and to be relieved once warfarin intake ceases.
- Warfarin binds heavily to plasma proteins (99%) so it’s very sensitive to Interactions with drugs which displace it.
- To treat warfarin overdose, give Vitamin K (takes time for effect) or fresh frozen plasma (immediate replenishment of factors).
- Heparin: anticoagulant which potentiates function of anti-thrombin III which inhibits thrombin; works fast, but must be given IV

**Sulfasalazine Case**
- Sulfasalazine a molecule of sulfapyridine linked to 5-aminosalicylic acid.
- Sulfasalazine travels to intestine where it is broken down by bacteria (which cleave the diazo bond), releasing the anti-inflammatory 5-aminosalicylic acid. Sulfasalazine is used in ulcerative colitis.
- Newer drugs based on the same idea: olsalazine (two 5 ASA put together), mesalazine, balsalazide

**Asthma Case**
- **Theophylline:** binds to and inhibits adenosine receptor which modulates adenylyl cyclase; reduced adenylyl cyclase activity results in less cAMP and hence less contraction/bronchoconstriction (this is just a proposed mechanism)
- **Cromolyn:** inhibits mast cell degranulation – of importance in asthma
- **Ipatropium:** anti-muscarinic used in asthma to relieve bronchoconstriction and inhibit pulmonary secretions
- **Beclomethasone, Fluticasone:** inhaled steroidal anti-inflammatory drug used in asthma
- **Zafirlukast, Montelukast:** antagonize cysteinyl leukotriene receptors
- **Zileuton:** Inhibit 5-lipoxygenase (which is first step in leukotriene production)

**Poison Case (look at case)**
- **Cyanide:** toxic chemical which binds to heme containing compounds; causes death by inhibiting a component of the electron transport chain in mitochondria thus preventing the use of oxygen in aerobic metabolism
- **Sodium Nitrite:** induces the conversion of hemoglobin to methemoglobin which has a high affinity for cyanide – allows one to suck up (“chelate”) cyanide quickly
- **Thiosulfate**: helps the enzyme rhodanese catalyze the conversion of cyanide to the less toxic thiocyanate.
- **Ethylene glycol**: toxic chemical found in antifreeze whose toxicity results from its metabolism to oxalic acid (stones!), glycolic acid, and glycoxilic acid; antidote is ethanol which competes for aldehyde dehydrogenase
  - *Fomepizole* (4-methyl pyrazole): alcohol dehydrogenase antagonist used as antidote to ethylene glycol or methanol (or other alcohol/glycol) poisoning.
- **EDTA**: a chelator used as an antidote to lead poisoning.
- **Digoxin**: blocks Na/K pump in the heart, producing an inotropic effect; one antidote is antibody to digoxin (*digibind*).
- **Ethanol, disulfiram**: disulfiram is used as a treatment in alcoholics; it inhibits the enzyme aldehyde dehydrogenase so that when ethanol is ingested and converted to acetaldehyde, the acetaldehyde builds up and produces a terribly uncomfortable effects (metronidazole has a disulfiram like effect).

**Thyroid Case**
- 1) Thyroid uptakes Iodine, 2) iodine is organified (thyroid peroxidase enzyme), 3) tyrosine residues of thyroglobulin (in colloid) are iodinated to form MIT and then DIT, 4) DIT are conjugated to form T4. 5) lysosomal proteolysis releases T4 from thyroglobulin. 6) peripheral conversion of T4 to T3 (more potent)
  - Endocrine control: negative feedback loops via free T3 and T4 at level of hypothalamus (TRH) and pituitary (TSH).
- **Grave’s disease**: anti-TSH receptor Ab; hyperthyroid state with low TSH.
- **Acute Thyrotoxicosis**: beta blocker to control sympathetic/cardiovascular effects, iodides, steroids to block peripheral T4 → T3, thioamides.
  - Organic anions perchlorate, SCN-, I--: block thyroid iodine uptake.
  - Block organification and iodine and iodification of thyroglobulin: thioamides (*PTU* and *methimazole*). Slow onset (weeks for thioamides), can use PTU in pregnancy (not methimazole because it readily crosses placenta).
  - Block proteolysis: iodides (blocks release of preformed hormone) [iodide also decreases size and vascularity of thyroid].
- **Long term**: anti-thyroid drugs, radioactive iodine ablation, thyroidectomy.

**Renal Failure case**
General recommendations for drug dosing in renal failure:
- **Use drugs not affected by renal disease or with a wide safety margin**: Adjust dose based on best estimate of GFR, measure serum levels & alter dosage based on individualized pharmacokinetics parameter (i.e. monitor your patient!).
- **Digoxin**: narrow therapeutic index - toxicity due to decreased Vd - maintain constant concentration by decreasing dose & keep the dosing interval the same.
- **Gentamicin**: decreased renal clearance in renal disease - maintain peak and trough concentration by keeping the dose the same and changing dose intervals (peak concentration maintains antibacterial power).

**Glaucoma Case**
- **engineering problem**: decrease aqueous humor by 1. increasing outflow or 2. decreasing production of aqueous humor.
Increase outflow: basically need cholinergic agonists, which acts as miotic agents and contract ciliary muscle which opens trabecular network and allows outflow. Can use direct agonists or acetylcholinesterase inhibitors.
- **Agonists:** 
  - Pilocarpine
- **Acetylcholinesterase inhibitors:** echothiophate

Decrease production
- **Beta blockers** (beta 1 selective): timolol. Antagonize beta receptors which stimulate production.
- **Carbonic anhydrase inhibitors** (acetazolamide) decrease HCO-3 levels which limits Na+/HCO-3 cotransport necessary for aqueous production.

**Antiemetics Case**
- Chemoreceptor trigger zone in brain stem "samples" toxic compounds in blood because of lack of strong blood brain barrier. Inhibit emesis by affecting various receptors in CTZ including 5HT, D, Ach, H…
- **Ondansetron, Granisetron, Dolasetron** (5HT3 antagonists): newest and quite powerful class of antiemetics, especially for chemo induced
- Dopamine antagonists (D2 primarily): some typical antipsychotics like prochlorperazine, also domperidone. Watch side effects of dopaminergic blockade.
- Scopolamine (M1 antagonist) and antihistamines (H1): for motion sickness
- Others: corticosteroids, cannabinoids, NK antagonists.

**Geriatric Pharmacology Case**
- Consider special problems in elderly: behavior and memory changes, financial hardships, confusion which may affect compliance and maintenance of therapy if symptoms dissipate, physical limitations, **loss of phase I metabolism, renal dysfunction, pharmacokinetics** (decreased lean body mass, body water, and albumin vs. slightly increased fat)
- **PPI:** no dosage adjustment necessary, but very expensive and patients may stop taking the drug when GI symptoms seem to resolve
- **Benzodiazepine:** Most benzos metabolized by phase I liver metabolism to generate pharmacologically active metabolites with long half lives. Elderly lose phase I metabolism and renal clearance capacity. Therefore, switch to benzos with little phase I dependent metabolism and **short** half lives to avoid build up of the benzo, i.e. oxazepam, temazepam, and lorazepam.

**Gout Case:** precipitation of uric acid
- **Indomethacin:** NSAID for acute analgesic and anti-inflammatory effects
- **Colchicine:** used for acute gout as anti-inflammatory agent by depolymerizing microtubules thus inhibiting leukocyte chemotaxis, diapodesis, and organelle degranulation
- **Allopurinol:** for chronic gout by inhibiting enzyme xanthine oxidase which limits production of uric acid
- **Probenecid (sulfipyrazone):** used in chronic gout. Inhibits reabsorption of uric acid from renal tubule. (Probenecid inhibits secretion of penicillin into tubule, so its concentrations remain high)

**Placental Transfer**
- Recall numerous pharmacokinetic changes in mother (increased blood volume, increased renal clearance and RBF, increased P450, decreased albumin concentration) and fetal pharmacokinetics
- Remember fetal toxicity in terms of organogenesis mainly in first twelve weeks. Can also get toxicity from drugs given near labor (i.e. dependence).
- **Phenytoin** (for epilepsy) can cause fetal hydantoin syndrome.
- **Verapamil** unclear toxicity
- **Thalidomide** (for morning sickness) caused phocomelia.
- **Panhypopituitarism**: patient given corticosteroid (also administered during stress of labor), fludrocortisone (mineralocorticoid replacement), and synthroid (thyroxine replacement)
  - Corticosteroids can decrease birth weight but uncertain long term impact.
  - Synthroid: without synthroid the child could experience adverse developmental effects in musculoskeletal, facial, and mental (cretinism)
  - Fludrocortisone: no evidence for fetal harm because aldosterone not regulated primarily by ACTH feedback mechanisms

**Alcohol: Ethanol**
- **Disulfiram** is used as a treatment in alcoholics; it inhibits the enzyme aldehyde dehydrogenase so that when ethanol is ingested and converted to acetylaldehyde, the acetylaldehyde builds up and produces a terribly uncomfortable effects (metronidazole has a disulfiram like effect)
- Lots of pathology to consider...
- Lots of biochemistry too...alcohol indirectly inhibits glycolysis, gluconeogenesis, beta oxidation while stimulating fatty acid synthesis. Mainly mediated by aberrantly high NADH/NAD+ ratio.
- Also consider effects of methanol and ethylene glycol in terms of alcohol oxidation.