CARDIAC PHARMACOLOGY REVIEW

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CARDIOVASCULAR AGENTS

Cardiotonic Agents

Drugs which increase force of myocardial (heart muscle) contraction
Enhance stroke volume and cardiac output
Also known as **inotropic agents**
Action
- Interfere with electrolyte entry/exit during depolarization
- Improve **cardiac output**

Indications
Treatment of **congestive heart failure (CHF)**
Used with diuretics, vasodilators, ACE inhibitors in CHF

Digitalis glycoside - Digoxin

Digoxin (Lanoxin) is most common agent - virtually the only one used
Monitor for **digoxin toxicity** - narrow therapeutic range (0.5-2.0 ng/ml)
Signs of toxicity
Anorexia, nausea/vomiting, yellow vision, fatigue, weakness, arrhythmias
Visual disturbance (esp blurred vision) **halo vison** (classic sign)
Elderly at risk for **toxicity**

Hold for **bradycardia** (HR >56) or tachycardia (HR >120) - sign of toxicity
Monitor electrolytes
Hypokalemia may potentiate toxicity
Overdose treated with **digoxin immune Fab** (antibody fractions specific for digitalis)

CARDIOTONICS

Digoxin (Lanoxin)
Amrinone (Inocor)
Milrinone (Primacor)
Digitoxin (Crystodigin)

milrinone is incompatible with IV furosemide (Lasix)
requires separate line

Antiarrhythmic Agents

Drugs that *effect myocardial conduction*
Classes: I, II, III, IV, misc unclassified agents
Etiology of arrhythmia determines choice of agent
Agents act to restore normal rhythm
Many agents in this class are **highly toxic** - need to closely monitor patient
Fatal dysrhythmias can occur from pro-arrhythmic effects of most agents
"Cure may be worse than diseases"
Overall relatively dangerous agents
Monitor patient for arrhythmias

COMMON ANTIARRHYTHMICS

Class IA
Quinidine (Quinaglute, Quinidex)
PAC, VCs V tachycardias, PAC, maintain NSR after cardioversion
Procainamide (Procan SR, Pronestyl, Procanbid)
- Same as quinidine; also ventricular dysrhythmias, WPW
- Associated with **drug-induced lupus-like reaction** with long-term use
- Other hematological reaction: agranulocytosis, neutropenia, thrombocytopenia, eosinophilia
Disopyramide (Norpace): PVCs, V-tachy, supraventricular tachycardia

Class IB
Lidocaine (Xylocaine) - ventricular dysrhythmias - frequently given IV bolus
Mexiletine (Mexitil) - toxic
Phenytoin (Dilantin) - used also for seizure control
Tocainide (Tonocard) - toxic

Class IC - **very toxic**
Flecainide (Tambocor)- V-dysrhythmias (life threatening) , paroxysmal a-fib, paroxysmal SVT
Propafenone (Rythmol) - life threatening V-arrhythmias, persistent a-fib

Class II - Beta-blockers (see separate section)

Class III - **toxic**, used as last resort - **life-threatening arrhythmias** unresponsive to other agents
Amiodarone (Cordarone) - very toxic; used where other drugs fail
Supraventricular-ventricular arrhythmias unresponsive to other drugs
Bretylium tosylate (Bretylol) - life threatening ventricular arrhythmias (ICU/CCU)
Dofetilide (Tikosyn) - maintain NSR with a-fib or a-flutter

Class IV - Calcium channel blockers (see separate section)

Unclassified
Adenosine (Adenocard): SVT, WPW
Short half-life - used IV emergency situations

Agents for Hypotension (Low Blood Pressure)

Adrenergic agonists primary agents - stimulate flight or flight in autonomic nervous system
Work in same manner as epinephrine to raise BP
B-adrenergic agonists (stimulation) must be used with caution in cardiogenic shock
Increased heart rate and contractility may increase O2 consumption
May predispose to arrhythmias

If **volume depletion** causes shock must **replace fluid** (volume) to restore BP
Indications: treatment of **shock or resuscitation**
Contraindicated hypovolemic shock (low blood volume) until replace fluid
Side effects: potentially **fatal arrhythmias** (from increased O2 demand)
Monitor BP; check renal output; titrate up or down - do not abruptly stop; normally ICU/CCU
Class members differ with respect to indications and therapeutic actions

COMMON ADRENERGIC AGONISTS

Epinephrine (Adrenalin)
Norepinephrine (Levophed)
Isoproterenol (Isuprel)
Dopamine (Intropin)
Dobutamine (Dobutrex)

Epinephrine (Adrenalin) - natural catecholamine; both alpha and beta activity
Increases HR, contractility, conduction speed
bronchodilation, gluconeogenesis
Used: cardiac arrest, anaphylaxis, status asthmaticus, bradycardia, (IV, IM, SQ)

Norepinephrine (Levophed) - naturally occurring catecholamine - primarily alpha
Intense vasoconstriction and PVR, increased contractility
Used only in shock refractory to other agents where need intense vasoconstriction
IV only - onset 1-2 minutes

Isoproterenol(Isuprel) - synthetic catecholamine; mostly B-adrenergic
Increases HR, contractility - stimulates more than epinephrine
Indications: bradycardia refractory to other agents
Contraindicated in routine treatment cardiac arrest; other agents used first

Dopamine (Intropin) - naturally occurring catecholamine - precursor to norepinephrine
Also functions as neurotransmitter
Increases force contraction, increase CO; minimal increase in HR - (less O2 demand)
Low dose = renal dose (1-2 ug/kg/min) - stimulates renal receptors
- Improves renal vasodilation
Intermediate dose 1 (2-10 ug/kg/min) stimulate B and dopaminergic receptors
Enhanced cardiac output, modest increase SVR,
Increased venous tone and central venous pressure

Intermediate dose 2 (10 ug/kg/min) predominately adrenergic activity
Renal, mesenteric, arterial and venous vasoconstriction
Marked increase in systemic SVR and pulmonary vascular resistence
High Doses (> 20 mg/kg/min) potent vasoconstriction similar to norepinephrine
Indications:
increase in renal perfusion of low output states **- renal failure, CHF**
Treatment of hypotension with bradycardia and no hypovolemia
Causes **tissue necrosis with extravasation**
Avoid peripheral line (vs central line)
Do NOT IV push

Dobutamine (Dobutrex) - synthetic catecholamine
- Dopamine derivative without vascular effects (does not bind to dopamine receptors)
- Potent inotropic effects (force) primarily beta receptors of myocardium
- Increases cardiac output; decreases PVR; increase HR (higher doses)
- Indications
  Pulmonary congestion with low cardiac output, hypotension with LV dysfunction, septic shock (improve LVF), CHF (systolic), cardiogenic shock (with dopamine)
- Nurse: use smallest effective dose during titration

Calcium Channel Blockers

- Block entry of calcium into calcium selective channels in cellular membrane
- Clinical effects
  - **Vasodilation** (reduces PVR thus reduces BP) , bradycardia, decreased force of contraction, reduced AV node conduction
  - Reduce oxygen consumption and myocardial energy demands

- Indications (clinical uses)
  - Management of **angina**
  - Mild to moderate **hypertension**
  - Cardiac **arrhythmias**
  - Cerebral **arterial spasms**, prevent **coronary spasm**
  - Management of **migraines**
- Cautious use with beta-blockers
- Contraindications: LV dysfunction, heart block, cardiogenic shock

- Misc considerations
  - Strongest chronotropic effect: verapamil
  - Most potent smooth muscle (vaso)dilator: nifedipine
  - Indicated for cerebral vasospasm nimodipine
  - **Reduction in BP due to decreased PVR**

Short acting agents are contraindicated - Do not administer (causes MI)
- We used to commonly give Procardia 10 mg sl to acute HTN - this is now considered malpractice to order such and most nurses will not carry out this order even if written

COMMON CALCIUM CHANNEL BLOCKERS

Class: **BENZOTHIAZEPINES**

Diltiazem (Cardizem**, Cardizem CD,** Cardizem SR, **Dilacor XR**, **Tiazac)**

Class: **DIHYDROPYRIDINE**

Nifedipine (Adalat CC, **Procardia XL), amlodipine (Norvasc) felodipine (Plendil)**, nimodipine (Nimotop), **nicardipine (Cardene, Cardene SR)**, **nisoldipine (Sular) isradipine (DynaCirc, DynaCirc CR)**

Class: **DIPHENYLAKYLAMINES**

Verapamil (Calan, **Calan SR,** Isoptin SR, **Covera HS**, Verelan, **Verelan PM**)

COMBINATION PRODUCTS: ACE-inhibitor and calcium channel blocker
Teczem (diltiazem and enalapril), **Tarka** (verapamil and trandolapril)
Lexxel (enalapril and felodipine) **Lotrel** (amlodipine and benazepril)

Beta Blockers

- Blocks action of catecholamines e.g. blocks adrenaline (epinephrine)
- **Blocks "fight or flight" response**
  Recall the "fight or flight" response = tachycardia, increased contractility, increased renin release (kidneys), bronchial dilation, K entry into cell

- Indications
  Hypertension, (reduces myocardial O2 need)
  Migraine prophylaxis**,**
  Supraventricular/ventricular arrhythmias, reduces **tachyarrhythmias**
  Glaucoma (reduce intraocular pressure)
  Hyperthyroid crisis and thyroiditis symptom management
  Acute MI and **angina**
  Stage fright and **public speaking anxiety** (not for athletes or dancers)
  Pheochromocytoma

- **Selective** (B1) vs **non-selective** (B2)
  B1 = heart; B2 = lungs (hint to remember: you have " 1 heart and 2 lungs"
  Selectivity lost at higher doses; prefer B1 if required use in asthmatic

- **Avoid** with bronchoconstriction and **asthma** (further constricts bronchioles)
- **Masks** signs of **hypoglycemia** - **cautious** use with **DM Type I** (may **mask insulin shock**)
- Previously contraindicated in heart failure; some agents now indicated for heart failure
- Commonly causes **impotence** and **fatigue/depression** - leads to non-compliance
- Worsens PVD (peripheral constriction); unfavorable glucose-lipid profile (**avoid in DM**)
- **Hold** dose for **bradycardia** (usually held for HR below 56)
- **Never discontinue abruptly!** (Rebound hypertension)

COMMON BETA BLOCKER AGENTS

NONSELECTIVE AGENTS - B2
- Nadolol (Corgard)
- Penbutolol (Levatol)
- Pindolol (Visken) B2
- **Timolol (**Blocadren**,** Timolide**, Timoptic *)**
- **Labetalol (Normodyne, Trandate**)
- **Propranolol (Inderal, Inderal LA)**
- **Carvedilol (Coreg)**
- Levobunolol (Betagan*)

SELECTIVE AGENTS - B1
- Acebutolol (Sectral) B1 selective
- Sotalol (Betapace) B1 selective
- Bisoprolol (Zebeta) B1 selective
- Betaxolol (Kerlone, Betoptic*) B1 selective
- **Atenolol (Tenormin**)- B1 - selective
- **Metoprolol (Toprol, Toprol XL** OptiPranolol*)

AGENTS IN COMBO WITH DIURETIC HCTZ **Tenoretic, Ziac, Lopressor HCT**, Inderide, Corzide - * OPTIC AGENTS for glaucoma

COMMENTS RE: INDIVIDUAL CLASS MEMBERS

Propranolol (Inderal):
Nonselective - commonly used in stage fright, migraine, HTN, nightmares
Atenolol (Tenormin)- selective agent, very commonly used
Labetalol (Normodyne, Trandate) B2 nonselective; both alpha1 and beta2 receptors
Used PO for routine **HTN**; also **IV for hypertensive crisis** (ICU/CCU)
Somewhat less impotence and other side effects
Carvedilol (Coreg): B2 nonselective used in heart failure and s/p MI
Previously BB were contraindicated in heart failure; thinking has changed and now they are not only used for pts with HF but mandated for use s/p MI. Contrary to previous thinking they causes reversal of neurohormonal stimulation which leads to LVF
Esmolol (Brevibloc): B1 selective and very short-acting (minutes)
Used IV only (ICU/CCU) for converting **a-fib**
Metoprolol (Lopressor, Toprol) selective agent - very commonly used
Glaucoma Agents:
Timolol (Timoptic), metoprolol (OptiPranolol), **levobunolol (Betagan**), betaxolol (Betoptic)

Nitrates (Nitroglycerine)

Improve blood flow to heart
Work via direct **relaxation of smooth muscle** causing **vasodilation**
Vasodilation results in reduced preload
Indications: **angina** (acute or long-term)
Effects of **reduced preload**
Reduces myocardial oxygen demand
Reduces left ventricular (LV) end diastolic volume (EDV)
Relieves coronary artery spasm
High doses reduces system vascular resistence (SVR) - thus useful to treat CHF

SL route is very common route (dissolve tab under tongue; spray under tongue)
SL results in rapid administration (1-2 minutes)
Can also be give IV, PO, **transdermal patch** or ointment (30-60 minutes)

Transdermal patch or **ointment**
Av oid contact with nurse's hands - causes **migraine-like headache**
Removed 8-10 hours qd (usually HS) to decrease toleration (decreased action)
Agents commonly cause **vascular headache** (similar to migraine)

IMPORTANT CONSIDERATIONS - NURSING IMPLICATIONS

- Results in **hypotension** (lowering BP) - monitor BP frequently
- Medicate prn for **headache** as ordered
- Never give to patient taking **sildenafil (Viagra)** - fatal interaction
- Cautious use with other drugs which can also lower BP:
  Alcohol, CaCh blockers, B-blockers, phenothiazine (Thorazine), haloperidol (Haldol)
- **SL NTG pills are very unstable** - keep in dark bottle; replace q 30 days
  Patient should feel "tingling" under tongue

- Issues with **topical administration** (patch or ointment)
  - Rotate sites - remove previous patch
  - Avoid contact with hands of nurse (headache)
  - Do not rub-in
- **Hypotension** is very common following therapy - monitor BP
- **Tolerance** to nitrates - nitrate-free interval is needed - usually 8-10 hrs HS

COMMON NITRATE PREPARATIONS

SL PREPS (acute attacks, prophylaxis)

Nitroglycerine SL tabs (1/150) Nitrostat (1/150)
Nitroglycerine spray (Nitrolingual)
Isosorbide dinitrate in SL tabs **(Isordil)**

IV PREPS: **Nitroglycerine IV (Tridil, Nitro-Bid IV)**

PO PREPS (prophylaxis only - not for acute attacks)

Nitroglycerine sustained-release (Nitrobid, Nitrong, Nitrospan)
Isosorbide mononitrate (**Imdur,** Ismo, Monoket**,** Tembids)
Isosorbide dinitrate
(Dilatrate-SR, Iso-Bid, Isonate, Isorbid, **Isordil**, Isotrate, **Sorbitrate)**

TRANSDERMAL (prophylaxis, not for acute attacks; remove HS to avoid tolerance)

Nitroglycerine transdermal patches
(Nitro-Dur, Nitro-bid, Transderm-Nitro, Nitro-Disc, Deponit, Minitran)

Angiotensin-Converting Enzyme (ACE) Inhibitors

Controls BP via **preventing conversion of angiotensin I to angiotensin II**
Kidney secretes renin -> angiotensin I -> angiotensin II
Angiotensin II is potent vasoconstrictor
Angiotensin II stimulates **aldosterone** release which **retains sodium and water**

Indications - **HTN** and **CHF - Diabetic nephropathy**
First line agent for CHF (previously diuretics and digoxin were first line agents)
Actually prevents and reverses left ventricular hypertrophy in CHF
One of most common agents for hypertension (low side effect profile)

Pharmacologic action

Prevents conversion angiotensin I to angiotensin II (inhibits needed enzyme)
Increases renal blood flow - promotes Na+/H20 excretion; reduces K+ excretion
Increases bradykinin release - vasodilation

IMPORTANT CONSIDERATIONS

Contraindicated for pregnancy - causes **fetal death** (renal agenesis)
Hypersensitivity is common esp **angioedema mouth/lip** and face
D/C if C/O tingling to lips - treatment is antihistamines and epinephrine
Bronchospasm, dyspnea
Dry cough is common annoying side effect for some people
DM - indicated for diabetics (renal blood flow) even if not hypertensive
CHF - first line therapy - "remodels" the failing ventricle
HTN - one of most commonly prescribed agents - "clean" side-effect profile
NSAIDs can decrease therapeutic effect
Retains potassium - avoid co-administration with K-sparing diuretics - **monitor K+**

ACE INHIBITOR PREPARATIONS

Benazepril (Lotensin)
Captopril (Capoten)
Fosinopril (Monopril)
Quinapril (Accupril)
Lisinopril (Prinivil)
Ramipril (Altace)
Enalapril (Vasotec)
Perindopril (Aceon)
Moexipril (Univasc)
Trandolapril (Mavik)

COMBINATION ACE-INHIBITOR PREPS

Combo with Diuretic (HCTZ)

Accuretic, Capozide, Lotensin HCT, Prinzide, Uniretic, Vaseretic, Zestoretic

Combo with Calcium Channel Blockers

Lexxel (enalapril and felodipine)
Lotrel (benazepril and amlodipene)
Tarka (trandolapril and verapamil)
Teczem (enalapril and diltiazem)

Angiotensin II Receptor Blocking Agents

- HTN also **CHF** (minor role used only where patient cannot take ACE)
- Action similar to ACE-inhibitors - blocks action of **angiotensin II** at tissue level
- Renin -> Angiotensin I -> Angiotensin II - X - **blocks action at tissues**
- Angiotensin II is potent vasoconstrictor - blocking it would relax vessels -> lower BP
- Effect on BP similar to ACE-inhibitors (lowers BP, treats HTN)
- **Not** usually associated with **dry cough** or **angioedema**
    Good choice for patients intolerant of these side-effects or allergic to ACE
    ACE is usually first choice due to somewhat better effectiveness
- Good **second choice for CHF** for patients who cannot take ACE
- **Contraindicated in pregnancy** (fetal death from renal agenesis)
- Widely prescribed for HTN - low incidence of side-effects - well tolerated
- Monitor for **hyperkalemia**

ANGIOTENSIN II BLOCKING AGENTS

Losartan potassium (Cozaar)
Valsartan (Diovan)
Irbesartan (Avapro)
Candesartan (Atacand)
Telmisartan (Micardis)

COMBO ANGIOTENSIN II BLOCKING AGENTS

Irbesartan-HCTZ	Avalide
Valsartan-HCTZ	Diovan-HCT
Losartan-HCTZ	Hyzaar
Candesartan-HCTZ	Atacand HCT
Telmisartan-HCTZ	Micardis-HCT

Alpha Adrenergic Blockers

Indication: **HTN** - some used also for **BPH**
Commonly used with diabetics: no unfavorable impact on CHO and lipid metabolism
    Actually has positive effect on lipids (decrease cholesterol/triglycerides; raise HDL
    No adverse effect on glucose, uric acid or potassium levels
First dose orthostatic hypotension
    - Common for patient to experience hypotension/syncope with first dosing
    - Usually **administered HS**
    - Use with **caution in the elderly** due to hypotension/syncope
    - Avoid use with diuretics (orthostatic hypotension)
Side effects: fatigue, weakness, nasal congestion, headache

ALPHA ADRENERGIC BLOCKERS

Doxazosin (Cardura) - also indicated for BPH
Prazosin (Minipress)
Terazosin (Hytrin) - also indicated for BPH

Prazosin and polythiazide (Minizide) - combination product with diuretic
Phenoxybenzamine (Dibenzyline) - nonselective - used for pheochromocytoma

Central Alpha Agonists

Indication: **HTN**; clonidine also used for **drug withdrawal**
Mechanism:
- Reduce sympathetic vasoconstriction
- Reduce peripheral vascular resistance (PVR)

- Older agents which are used less frequently today
  Exception is **clonidine (Catapres)** - available as **patch** for HTN and drug withdrawal
  Exception: **methyldopa (Aldomet)** first choice for **pregnant patient with HTN**

- **Abrupt withdrawal** causes **rebound hypertension**
- Can cause **orthostatic hypotension** in **elderly**
- Common side effects are dry mouth, sedation, bradycardia and withdrawal hypertension.

CENTRAL ALPHA AGONISTS

Clonidine (Catapres) also available as transdermal patch (**Catapres TTS**)
Guanabenz acetate (Wytensin)
Guanfacine Hcl (Tenex)
Methyldopa (Aldomet) - hepatic and autoimmune-like disorders

COMBINATION PRODUCTS WITH DIURETIC

Methyldopa and HCTZ (Aldoril)
Clonidine and chlorthalidone (Combipres)

Older - Infrequently Used Antihypertensive agents

PERIPHERAL ADRENERGIC INHIBITORS

- Mechanism: prevents release or norepinephrine in response to sympathetic stimulation
- Interactions: displaced by indirect-acting sympathomimetics and tricyclic antidepressants
- Side effect profile: **orthostatic hypotension**, fluid retention, **diarrhea**, bradycardia

PERIPHERAL ADRENERGIC BLOCKERS

Guanadrel sulfate (Hylorel)
Guanethidine monosulfate (Ismelin)
Reserpine (Serpasil)

DIRECT VASODILATORS

Hydralazine (Apresoline)
Minoxidil (Loniten)

DIRECT VASODILATORS

- After load reducing agents
- **Hydralazine (Apresoline**) - associated with **lupus-like syndrome**
- **Minoxidil (Loniten)** - associated with hirsutism - also used to treat alopecia (baldness)

Cerebral and Peripheral Vascular Dilating Agents

Cause **direct vasodilation** of blood **vessels**
Therapeutic effect differs depending on tissue and actual vessels involved
    Artery (deliver oxygen) vs veins (remove unoxygenated blood)
    May differentially effect segments within same vascular bed
Indications:
    - **HTN, atherosclerosis:** coronary (angina) or cerebral (TIA)
    - Peripheral vascular constriction**: intermittent claudication**, **severe ischemia**
Action: **relax smooth muscle**; **interfere** with sympathetic-mediated **vasoconstriction**
Effect: **improve blood flow** in peripheral vascular tissue

CEREBRAL AND PERIPHERAL VASODILATING AGENTS

Isoxsuprine (Vasodilan, Voxsuprine)
Papaverine (Pavabid)
Dipyridamole (Persantine) - used to prevent TIA; also s/p valve replacement
Cyclandelate (Cyclen, Cyclospasmol)
Pentoxifylline (Trental)

Pentoxifylline (Trental) - xanthine derivative - **affects blood viscosity**
    - Increases **microcirculation** - enhances **tissue oxygenation**
    - Indication: **intermittent claudication** from occlusive arterial disease
    - Onset 2-4 wks; clinical manifestations: at least 8 wks
    - **Contraindicated: cerebral or retinal hemorrhage**
    - Side effects:
        H/A, dizziness, blurred vision, n/v, dyspepsia, dyspnea, edema, hypotension, edema, epistaxis, flulike symptoms, belching/bloating

Diuretics

Promote **loss of body fluids** via increasing fluid lost through **renal system**
Classes of agents
- **Loop diuretics**: potent - act in distal Loop of Henle
- **Thiazide** and thiazide-like: act between ascending loop of Henle and early distal tubule
- **Potassium-sparing**: act on late portion of distal convoluted tubule and collecting duct
- **Carbonic anhydrase inhibitors**: proximal nephron
- **Osmotic agents:** proximal nephron

Action: alter **balance of sodium and water in renal tubules**
- Sodium loss accompanied by osmotically equivalent amt water ("water follows sodium")
- Increased electrolyte excretion - can result in hypokalemia (low potassium)

Indications: **HTN, edema, CHF**, **intracranial** or **ocular pressure**, electrolyte disorders

IMPORTANT CONSIDERATIONS

Fluid/electrolyte imbalances - common sequelae
- **Loop diuretics** greatest potential to **alter electrolyte esp K+**
- IV route has greater potential vs PO
- **Elderly** particularly prone to imbalance and **hypokalemia**

Monitor urine output; daily weights; avoid HS administration
Reduce clearance of **lithium** - predisposes to **toxicity**

Carbonic Anhydrase (CAH) Inhibitors

CAH (enzyme) found in brush border of proximal tubule epithelial cell
CAH inhibitors derivatives of sulfonamide antibiotics
Limited usefulness: tolerance develops as HCO2 decline/metabolic acidosis development
Indications:
- Mountain sickness (rapid elevation), **glaucoma**, massive edema with metabolic acidosis (lowers bicarbonate level)

Acetazolamide (Diamox) - **glaucoma**, drug-induced edema (q other day)

Osmotic Diuretics

Mechanism
- Pull water into vascular space through high osmotic concentration
- Water so pulled is then excreted via urine

Indication
- Reduce **cerebral** and **intraocular pressure** (esp acute **glaucoma emergency**)
- Treat acute chemical poisoning - increased renal excretion toxins
- Prevent oliguric renal failure
- Hemolytic transfusion reaction (protect renal blood flow)

Side effects
H/A, blurred vision, confusion, convulsion, hypotension, angina-like pain, tachycardia, CHF, dermatologic rashes, n/v, diarrhea, marked diuresis, dry mouth, fever, chills, rhinitis, electrolyte imbalance, acidosis

Mannitol (Osmitrol): cerebral edema - check syringes for crystallization

Loop Diuretics

Potent diuretics - considered high-ceiling diuretics (peak effect greater than other diuretics)
Mechanism
- Weak acids which bind to plasma proteins
- **Blocks sodium-potassium-chloride cotransport** in **loop of Henle**
  - Impairs sodium reabsorption
  - Decreased osmolarity of interstitial tubes surrounding collecting ducts
  - Impedes ability of kidneys to concentrate urine
  - Result is **excretion of large quantities of urine with high levels of sodium**
  - **Increases potassium**, magnesium, calcium **excretion**
- Increase blood flow to renal medulla - **increasing fluid through kidney** and urine flow
- Systemic hemodynamic effects
  - Increased venous capacitance which reduces left ventricular filling pressure
  - Relieves **pulmonary edema**

Indications:
- Severe edema with **pulmonary edema, CHF**, hepatic cirrhosis, renal disease
- Treatment of HTN
- Ascites from lymphedema, malignancy, idiopathic edema
- Acute hypercalcemia (furosemide)
- Severe symptomatic hyponatremia

Side effects (most important/common ones)

Hearing loss/tinnitus, visual disturbance, **orthostatic hypotension**, **ECG** changes, rashes, exfoliative dermatitis (rare), hepatic dysfunction/alteration LFT, blood dyscrasias (rare), **fluid and electrolyte imbalance**, abnormal glucose tolerance (GTT), muscle cramping

LOOP DIURETICS

Furosemide (Lasix)
Bumetanide (Bumex)
Ethacrynic acid (Edecrin)
Torsemide (Demadex)

Thiazide Diuretics - Thiazide-Like Diuretics

- Possess weak CAH inhibitory activity
- Enhance action of antidiuretic hormone via sodium depletion - useful in **diabetes insipidus**

Mechanism
- Inhibit Na reabsorption in early distal tubules -> increase urinary excretion Na+
  - Water follows the excreted Na+
  - Also excreted is K+, magnesium, HCO3 (bicarbonate)
- Other actions
  - Augment calcium absorption in distal tubules
  - Relax arterial smooth muscle, reduce peripheral vascular resistance
  - Interfere with insulin release

Indications

CHF (mild to moderate), **HTN,** idiopathic hypercalcinuria (with renal calculi), nephrogenic diabetes insipidus, **edema** (hepatic cirrhosis, renal dysfunction, estrogen/steroid therapy)

Side effects (most important ones)

Orthostatic hypotension, light-headedness, **fatigue**, blurred vision, PVC, rash, photosensitivity, blood dyscrasia/marrow suppression (rare), muscle weakness, cramps, impotence, hyperglycemia, hyperuricemia, **hypokalemia**, increased BUN, **unfavorable lipid-CHO effects**

THIAZIDE DIURETICS

Chlorthalidone (Hygroton)
Hydrochlorothiazide (HydroDIURIL, Microzide, Esidrix)
Indapamide (Lozol)
Metolazone (Mykrox, Zaroxolyn)
Methyclothiazide (Enduron)
Chlorothiazide (Diuril)

ADDITIONAL CONSIDERATIONS

- Unfavorable lipid and CHO effects - **caution with DM**
- **Hydrochlorothiazide** most common **combination agent** in antihypertensive agents
  Combination products with beta-blockers, ace-inhibitors, angiotensin II blockers
- Monitor for **hypokalemia**
- Less potent than loop diuretics; commonly used in out-patient setting

Potassium-Sparing Diuretics

Not potent diuretics when used alone - can result in **hyperkalemia**
- Sometimes used in combination preps with thiazide diuretics
- **Contraindicated with ace-inhibitor** therapy - predisposes to hyperkalemia

Mechanism
Act on distal nephron to inhibit sodium absorption and potassium secretion

Indications
Adjuvant therapy with other diuretics - **minimize K+ loss**
Edema (CHF, cirrhosis, nephrotic syndrome)

Side effects (most important ones)

Photosensitivity/rash, liver enzyme abnormalities, blood dyscrasia, azotemia, increased BUN/creatinine, electrolyte abnormalities

ADDITIONAL CONSIDERATIONS

Monitor for hyperkalemia
Acute **renal failure** if **triamterene** is given with **indomethacin**
Increases serum digitalis levels; **hyperkalemia** with ACE-inhibitor therapy; **lithium toxicity**

POTASSIUM-SPARING DIURETICS

Amiloride (Midamor)
Spirolactone (Aldactone)
Triamterene (Dyrenium)

DIURETIC COMBINATIONS

Triamterene/HCTZ (Dyazide, Maxzide)
Amiloride/HCTZ (Moduretic)
Spirolactone/HCTZ (Aldactazide)

Lipid Lowering Agents

Goal lipid lowering agents - **change lipid profile** with minimal side effects
Many lipid-lowering agents are **hepatotoxic**
Lipid profile goals
- Lower: total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDH)
  - LDL: "bad cholesterol" - promotes atherosclerosis
  - **LDL: most significant factor in disease development**
- Raise or maintain: **high-density-lipoprotein (LDH**) "good cholesterol"

American Heart Association (AHA) goals re lipids
- **LDL under 100 mg/dl** for cardiovascular disease or 2 or more risk factors ASHD
- **LDL under 130 mg/dl** for individuals without risk factors ASHD
- **TG** should be kept **under 200 mg/dl**; **HDL** should be **over 35 mg/dl**

Indications
- Decision to initiate therapy based on lipid profile with consideration to risk factors
- Pharmacologic therapy to be used in conjunction with diet and life-style modification

Monitor liver function testing (LFT) before and during therapy
- Monitor q 6 wks x 3 months; q 8 weeks remainder of first year
- Check q 6 months after first year
- D/C medication if LFT elevated esp 3X normal

Bile acid-sequestering resins

Mechanism
- Decrease resorption of bile -> enhances oxidation of cholesterol to form bile
- Decrease serum TC and LDL
- Cholesterol required for formation of bile acids (secreted into intestines during digestion)
- Majority of bile acids secreted are reabsorbed from intestines (enterohepatic circulation)
- Resorption is prevented when bile-acids combine with sequestrants (insoluble complex)

Indications
- Reduction of elevated TC/LDL
- Only lipid-lowering agents **appropriate for individuals with active liver disease**

Drug interactions
- **Decrease absorption of other medications**

BILE ACID SEQUESTRANTS

Cholestyramine
(Prevalite, Questran, Questran Lite)
Colestipol HCl (Colestid)
Colesevelam (Welchol)

Side effects (most important ones)
- **Constipation, fecal impaction**, abdominal discomfort, flatulence, myalgia-arthralgia, vitamin deficiency with long-term use (A, D, K)

ADDITIONAL CONSIDERATIONS
- Prevent constipation with fiber, etc.
- Life style issues with multiple dosing of unpalatable medications
- Scheduling other meds can be challenging (co-administration is contraindicated)

HMG-CoA Reductase inhibitors - "Statins"

Work on enzyme system - mainstay to lipid lowering therapy
Contraindicated in liver disease - caution with ETOH abuse or history of liver disease
Therapy requires **liver function monitoring**
Rhabdomyolysis can occur esp if used with other lipid lowering agents
CPK to monitor for rhabdo if suspicious
D/C therapy with complaints of muscle pain

Mechanism
HMG-CoA reductase is required for cholesterol synthesis
HMG-CoA reduces LDL and precursor VLDL (very low density lipoprotein)
May contribute to LDL catabolism
Decrease serum TC and LDL via decreasing production and increasing catabolism

Indications:
Reduction of elevated TC and LDL
Reduction of elevated LDL in presence of hypertriglyceridemia

Side effects: (important ones)
Elevated LFT esp transaminase levels, **myalgia,** myopathy, **rhabdomyolysis,** skin reactions

Contraindicated for pregnancy (category X)

HMG COA REDUCTASE INHIBITORS

Lovastatin (Mevacor)
Pravastatin sodium (Pravachol)
Simvastatin (Zocor
Atorvastatin (Lipitor)
Fluvastatin (Lescol**)**

Nicotinic Acid (Niacin)

Mechanism:
- Decreases synthesis of LDL via reducing hepatic synthesis of VLDL
- Increases synthesis of HDL, inhibiting lipolysis of adipose tissue; increases lipase

Indications
- Good for low HDL; high triglycerides or both
- Most effective RX for raising HDL (15-30%)
- Indications: LDL 100-129 plus HDL less than 40

NICOTINIC ACID
Niacin (Nicobid, Nicolar)

Side effects are quite significant: increase dose gradually to minimize
Skin flushing/itching; GI disturbance, activation of peptic ulcer disease; **induces GB disease (**very common) - **hepatotoxicity,** hyperuricemia; glucose intolerance: avoid with DM, atrial fibrillation , hypotension, transient H/A

OTHER CONSIDERATIONS

- Causes **marked skin flushing** (transient) in 30 min
- Extended release has less flushing but higher incidence of hepatotoxicity
- **ASA 325** 30-40 min previous may minimize flushing; antihistamine decreases pruritus
- Contraindicated liver or GB disease; caution ETOHics, gout, diabetes, peptic ulcer
- Does not require RX - can purchase OTC and pt can thus induce gall bladder disease

Fibric Acid

Mechanism:

- Increase clearance of VDRL cholesterol via enhancing lipolysis
- Reduces hepatic cholesterol synthesis.

Effectiveness

- **Lowers triglyceride** 20-50%; raise HDL up to 20%; reduce LDL 5-15%*

Indications

- Severe hypertriglyceridemia (>150) - lowers 15-30%
- Increases HDL; *not effective for lowering LDL*
- **Particularly useful for DM** and familial beta-lipoproteinemia

FIBRIC ACID

Gemfibrozil (Lopid)
Clofibrate (Atromid-5)
Fenofibrate (Tricor)

Side Effects: can be quite significant

Nausea, bloating, flatulence, abdominal distress, **liver-function abnormalities**. **Myositis**, gallstones, elevation of LDL has been reported, **malignancy with clofibrate,** GB disease**,** hematologic abnormalities

In **combo with "statin**" there is greatly **increased risk for myopathy**
Clofibrate rarely if ever used - very toxic; **risk of hepatic malignancy** , serious GB disease
Fenofibrate (Tricor) newest agent - reportedly somewhat less toxic