CVS pharmacology

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Antiarrhythmic Drugs

- **CLASS I: Na+ CHANNEL BLOCKERS**
  - **Class 1A**
  - **Class 1B**
  - **Class 1C**
- **CLASS II: BETA BLOCKERS**
- **CLASS III : K+ CHANNEL BLOCKERS**
- **CLASS IV : Ca+ CHANNEL BLOCKERS**
- **UNCLASSIFIED**

CLASS I: Na+ CHANNEL BLOCKERS

CLASS I A

- block fast Na channels
- Preferentially in the open or activated state-"state-dependent" blockade
- Increase action potential duration (APD) and effective refractory period (ERP)
- Also have some K+ channel blocking action

Quinidine

- Other effects :
  - In addition to the above, causes M-block, which can increase HR and AV conduction.
  - May also cause vasodilation via alpha block with possible reflex tachycardia.
- Use:
  - Orally effective
  - wide clinical use in many arrhythmias; in atrial fibrillation,
  - need initial digitalization to slow AV conduction.
- Adverse effects:
  - nausea and vomiting,
  - cinchonism (GI disturbance, tinnitus, ocular dysfunction, CNS excitation),
  - Hypotension
  - prolongation of QRS and T QT interval associated with syncope (torsades).

- Drug interactions: hyperkalemia enhances effects and vice versa; displaces digoxin from tissue binding sites, enhancing toxicity; may oppose effects of AChE inhibitors in myasthenia.

Procainamide

- Less M block than quinidine and no alpha block, but more cardio depressant.
- Orally effective, often substituting for quinidine. Metabolized via N-acetyltransferase (genotypic variation) to N-acetyl procainamide (NAPA), an active metabolite, which prolongs APD.
- With IV use, this is less likely to occur.
- Adverse effects: systemic lupus erythematosus (SLE)-like syndrome (30% incidence); more likely with slow acetylators, hematotoxicity (thrombocytopenia, agranulocytosis), CNS effects (dizziness, hallucinations), CV effects (torsades).

Class 1 B

- Block fast Na channels (Decrease I_{NA},).
- Less state-dependent, block inactivated channels-preference for tissues partly depolarized (slow conduction in hypoxic and ischemic tissues).

Lidocaine

- IVuse in arrhythmias post-MI, during open heart surgery, or due to digitalis;
- drug of choice (DOC) for arrhythmias following attempted cardioversion.
- Clearance depends markedly on liver blood flow, and rapid first-pass effects preclude oral use.
- Adverse effects: CNS toxicity culminating in seizures in severe Over Dose.
- Least cardiotoxic of conventional antiarrhythmics.

- **Phenytoin**
  - An anti-seizure drug, used occasionally in digitalis OD to reverse AV block.
- **Mexiletine and Tocainide**
  - Orally active drugs, otherwise similar to lidocaine.

Class 1 C

- block fast Na channels especially His-Purkinje tissue.
- No effect on APD.
- No ANS effects

- **Flecainide and Encainide**
  - Limited use because of pro-arrhythmogenic effects leading to T sudden death post-MI and when used prophylactically in VT.

CLASS II: BETA BLOCKERS

- Decrease SA and AV nodal activity.
- Decrease Slope of phase 4 (diastolic currents) of AP in pacemakers.
- Prevent Beta-l adrenoceptor activation
- nonselective : Propranolol
- cardio selective drugs: acebutolol, metoprolol, and esmolol
- Antiarrhythmic uses: prophylaxis post-MI and in supraventricular tachyarrhythmias (SVTs);
- esmolol (IV) is used in acute SVTs.

CLASS III: K+ CHANNEL BLOCKERS

- Increase APD and ERP, especially in Purkinje and ventricular tissues.
- Decrease Ik (delayed rectifier current) slowing phase 3 (repolarization) of AP.

- Bretylium
  - IV use (backup) in life-threatening ventricular arrhythmias.
  - Releases amines and is pro-arrhythmogenic (torsades).

- Amiodarone
  - Activity mimics all antiarrhythmic drug classes (I, II, III, and IV); blocks Na, Ca, and K channels and beta adrenoceptors.
- Increase APD and ERP in all cardiac tissues.
- Half-life 30 to 60 days.
- Effective in a wide range of atrial and ventricular arrhythmias.
- Adverse effects:
  - Pulmonary fibrosis
  - corneal deposits
  - blue pigmentation ("smurf" skin)
  - photoxicity,
  - thyroid dysfunction
  - Increase LDL-C
  - Torsades
  - hepatic necrosis
- Drug interactions: Decrease clearance of digoxin, phenytoin, quinidine, theophylline, and warfarin

Sotalol

- Increase APD and ERP (Decrease Ik delayed rectifier current), and
- Also acts as a blocker to decrease HR and AV nodal conduction.
- Approved for prophylaxis in life-threatening ventricular arrhythmias.
- Adverse effects: lassitude, impotence, depression, torsades, AV block.

CLASS IV
Ca^{2+} CHANNEL BLOCKERS

- Decrease SA and AV nodal activity.
- Decrease Slope of phase 4 (diastolic currents) of AP in pacemakers.

Verapamil

- Prototype Ca^{2+} channel blocker
- Cardio selective, but also blocks vascular Ca^{2+} channels and cause hypotension and possible reflex tachycardia (blunted). Diltiazem is similar to verapamil.
- Prophylaxis in reentrant nodal and atrial tachycardias-not Wolff-Parkinson-White syndrome (WPW)
- Avoid in VT, as may progress to VF.
- Adverse effects: GI distress, dizziness, flushing, hypotension, AV block, CHF-avoid use concomitantly with beta blockers.

UNCLASSIFIED

Adenosine

- Decrease SA and AV nodal activity and Increase AV nodal refractory period.
- Activates A-receptors → causes Gi-coupled decrease in CAMP → increase K efflux, causing membrane hyperpolarization.
- DOC for PSVTs and AV nodal arrhythmias; used IV, half-life less than 30 seconds.
- Possible flushing, sedation, and dyspnea; antagonized by theophylline.

Magnesium

- Possible use as antiarrhythmic agent in torsades.
- Note that most of the antiarrhythmic drugs that block K channels associated with the delayed rectifier current have been implicated in torsades de pointes arrhythmias.
- Other drugs associated with prolongation of the QT interval include cisapride, erythromycin, thioridazine, and tricyclic antidepressants

Antihypertensive Drugs

- **SYMPATHOLYTICS / SYMPATHOPLEGICS**
- Decrease Sympathetic tone
- **Drugs Acting in the CNS**
- **Methyldopa**
- Pro-drug converted to a-methyl-NE, which activates presynaptic a2 adrenoceptors in the medulla to vasomotor outflow, mainly lowers PVR.
- Used in mild-to-moderate HTN.
- Adverse effects: sedation, dizziness, decreased libido, edema, positive Coombs' (hemolysis).
- Safe in renal dysfunction and in pregnancy.

Clonidine

- Also activates presynaptic *a2 adrenoceptors in the medulla -→ Decrease vasomotor outflow.*
- Used in mild-to-moderate HTN (patch causes fewer side effects)
- and also used in dependency states such as opioids or nicotine (withdrawals)
- Adverse effects:
  - dry mouth
  - Sedation
  - Insomnia
  - Edema
  - Bradycardia
  - On abrupt withdrawal:
    - Severe rebound HTN
- Drug causes mild postural hypotension which generally do not require discontinuation of drug
- but water retention may warrant concomitant diuretic use.

Adrenergic Neuron Blockers

- Reserpine
  - Causes destruction of storage granules in peripheral and central nerve endings → decrease NE in sympathetic neurons → decrease CO and PVR.
  - In CNS, decrease NE, DA, and 5HT.
- Adverse effects: mild orthostatic hypotension, fluid retention, sedation, depression (often severe), increase GI secretions.

Guanethidine

- Binds to storage granules to inhibit NE release. Accumulated into nerve endings - actions decreased by TCAs.
- Adverse effects: diarrhea, fluid retention (need diuretics), orthostatic hypotension, sexual dysfunction

Alpha Blockers

- Decrease arteriolar resistance and increase venous capacitance; initial reflex increase HR, but ultimately vasodilation with decrease PVR persists-no change in Renal Blood Flow.

Prazosin, Doxazosin and terazosin

- *all are selective blockers*
- Also used in BPH, increasing urinary flow by decreasing the tone of urinary sphincters.
- Adverse effects: "first-dose" syncope, orthostatic hypotension, urinary incontinence (especially in women).
- No adverse effects on plasma lipids-(may even be beneficial!!)

Beta Blockers

- Decrease BP-long-term mechanism unclear, probably decrease CO, but decrease PVR in some patients.
- **Propranolol**
- Prototype drug, but many other beta blockers are used in HTN
- All appear to be equally effective with respect to HTN.
- European American patients respond better than African American; young better than old.
- Adverse effects: CV depression, fatigue, sexual dysfunction, and with chronic use → Increase low-density lipoprotein cholesterol (LDL-C) and TGs
- Nonselective drugs may cause problems in asthmatics and diabetics and in PVD. Watch for rebound HTN on abrupt withdrawal

DIRECT-ACTING VASODILATORS

- Hydralazine
- Decrease PVR via arteriolar dilation-mechanism likely to involve the NO
- Decrease Resistance in coronary, renal, and cerebral beds; less in skin and muscle vessels.
- Used in moderate-to-severe HTN-orally active, metabolized by N-acetyltransferase with genotypic variation.
- Adverse effects: headache, flushing, sweating, fluid retention (use diuretic), reflex tachycardia (use beta blocker), SLE-like syndrome in slow acetylators.

Nitroprusside

- Decrease PVR via dilation of both arterioles and venules. Mechanism involves stimulation of guanylyl cyclase → Increase cGMP via release of NO
- Given by IV infusion in hypertensive emergencies (DOC)
- forms thiocyanate and cyanide ions, which can cause toxicity (cyanosis, muscle spasms, toxic psychosis) with infusion >12 hr.
- Can increase renin secretion.
- Rebound HTN may occur after even a short infusion.

Minoxidil

- Pro-drug that on sulfation opens K+ channels, causing membrane hyperpolarization → arteriolar vasodilation.
- Potent renal vasodilator increase renin.
- Used in moderate-to-severe HTN-orally active.
- Adverse effects: headache, flushing, sweating, fluid retention (use a diuretic), reflex tachycardia(use a beta blocker), possible pulmonary HTN due to volume shifts, hypertrichosis (clinical use, topically).

Diazoxide

- Arteriolar vasodilation via K+ channels opening. Reflex tachycardia → Increase Cardiac output. Increase Renin secretion.
- Used IV for hypertensive emergencies.
- Adverse effects:
  - Fluid retention (use diuretic)
  - Tachycardia (use a beta blocker)
  - Hyperglycemia via decrease insulin release
- Other uses: Insulinoma

CALCIUM CHANNEL ANTAGONISTS (CCAs)

- Block L-type Ca^{2+} channels in both cardiac and vascular tissues → Decrease Intracellular Ca^{2+} → Decrease contractility
- Vasodilation especially in arterioles and coronary vessels, plus natriuretic renal effects.
- African American patients and elderly patients respond well.

Verapamil and diltiazem

- More effects on heart than dihydropyridines (e.g., nifedipine)-possible AV block at high doses.
- Nifedipine may cause reflex tachycardia-possible arrhythmias/MI from rapid-onset forms.
- Nimodipine is used for subarachnoid hemorrhage-prevents vasospasm.
- Adverse effects: constipation, headache, gingival overgrowths (dihydropyridines in general), proteinuria (dihydropyridines in general), inhibition of P-glycoprotein drug transporter (only verapamil).
- No effects on plasma lipids.

ACE INHIBITORS AND AT-1 RECEPTOR ANTAGONISTS

- ACE inhibitors (ACEIs) (e.g., captopril) inhibit kininase II (angiotensin-converting enzyme), blocking the formation of angiotensin II and preventing its activation of AT-1 receptors in the adrenal cortex → decrease aldosterone and its effect on vasculature → decreasing vasoconstriction. ACEIs also inhibit the metabolism of bradykinin (BK), which causes NO-mediated vasodilation → Decrease PVR.
- AT-1 receptor antagonists (e.g., losartan) block the effects of angiotensin II but do not affect BK levels or enhance its effects.

DIURETICS

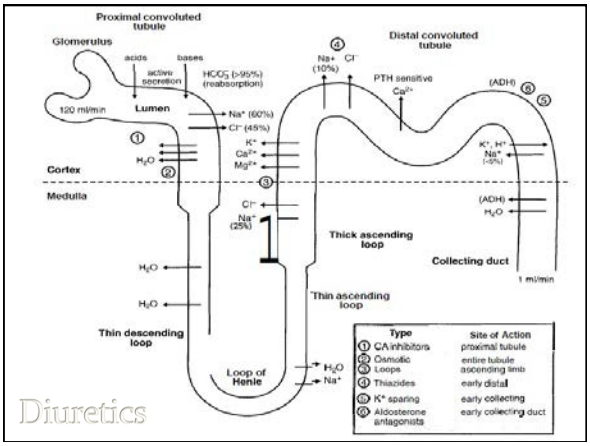
- The pharmacology of diuretics is described later in a separate section. Both thiazide and loop diuretics are commonly used in the management of HTN.
- For the initial drug management of mild-to-moderate hypertension, the Joint National Committee (JNC) report VI recommends either a beta blocker or a thiazide diuretic as the drugs of first choice.

Drugs for Heart Failure

- Decrease preload-diuretics, ACEIs, AT-1 receptor antagonists, and vasodilators.
- Decrease afterload-ACEIs, AT-1 antagonists, and vasodilators.
- Increase contractility-digitalis, beta agonists, and bipyridines.

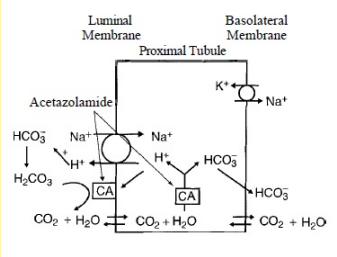
Antianginal Drugs

- Increase oxygen delivery by decreasing vasospasm (nitrates and CCBs).
- Decrease oxygen requirement by decreasing PVR, CO, or both (nitrates, CCBs, and beta blockers).



Diuretics

Carbonic Anhydrase Inhibitors

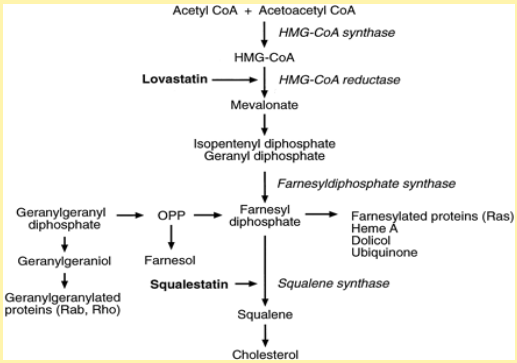


Antihyperlipidemics

- **BILE ACID SEQUESTRANTS**
  - Cholestyramine and colestipol are resins that complex bile salts, preventing their reabsorption from the GI tract → Increase synthesis of new bile salts → Decrease liver cholesterol → Increase LDL receptors → Decrease plasma LDL.
  - Not used in hypertriglyceridemias because they increase VLDL and TGs.
- Adverse Effects
  - Bloating, constipation, decrease absorption of digoxin, thiazides, tetracyclines, warfarin, and vitamin K.

HMG-CoA REDUCTASE INHIBITORS

- Lovastatin and the other "statins" inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.
- **Adverse Effects**
  - Diarrhea, myalgia/myopathy (watch CK), rhabdomyolysis (increase with gemfibrozil and nicotinic acid), increase LFTs, possible enhanced toxicity with P450 inhibitors.
  - SLE-like syndrome has been reported.



NICOTINIC ACID

- Inhibits VLDL synthesis and apoprotein synthesis in hepatocytes
- Increase HDL → **Decrease plasma VLDL,** LDL, and TGs
- Adverse Effects
  - Flushing and pruritus (use aspirin [ASA]), rashes, hyperuricemia, hyperglycemia, hepatotoxicity,
  - GI ulcer exacerbation.

Gemfibrozil

- Activates lipoprotein lipases, which promotes catabolism of VLDL and IDL → Decrease plasma VLDL, TGs, and LDL and causes small increases in HDL.
- Adverse Effects
  - GI distress, rash, gallstones, hypokalemia, myositis; potentiates warfarin and sulfonylurea hypoglycemic

Erythema Nodosum

- http://emedicine.medscape.com/article/1081633-overview
- Currently, the most common cause of erythema nodosum is streptococcal infection in children and streptococcal infection and sarcoidosis in adults.[3] Numerous other causes have been reported.[4] The causes reported most often in the literature are as follows:

- Bacterial infections: Streptococcal infections are one of the most common causes of erythema nodosum. Tuberculosis was an important cause in the past, but it has decreased dramatically as a cause for erythema nodosum; however, it still must be excluded, especially in developing countries.[5,6] *Yersinia enterocolitica* is a gram-negative bacillus that causes acute diarrhea and abdominal pain; it is a common cause of erythema nodosum in France and Finland.[7,8,9] *Mycoplasma pneumoniae* infection may cause erythema nodosum. Erythema nodosum leprosum clinically resembles erythema nodosum, but the histologic picture is that of leukocytoclastic vasculitis. Lymphogranuloma venereum may cause erythema nodosum. *Salmonella* infection may cause erythema nodosum. *Campylobacter* infection may cause erythema nodosum.

- Fungal infections: Coccidioidomycosis (San Joaquin Valley fever) is the most common cause of erythema nodosum in the American Southwest. In approximately 4% of males and 10% of females, the primary fungal infection (which may be asymptomatic or involve symptoms of upper respiratory infection) is followed by the development of erythema nodosum. Lesions appear 3 days to 3 weeks after the end of the fever caused by the fungal infection. Histoplasmosis may cause erythema nodosum. Blastomycosis may cause erythema nodosum.

- Drugs: Sulfonamides and halide agents are an important cause of erythema nodosum. Drugs more recently described to cause erythema nodosum include gold and sulfonylureas. Oral contraceptive pills are implicated in an increasing number of reports.
- Enteropathies: Ulcerative colitis and Crohn disease may trigger erythema nodosum. Erythema nodosum associated with enteropathies correlates with flares of the disease. The mean duration of chronic ulcerative colitis before the onset of erythema nodosum is 5 years, and erythema nodosum is controlled with adequate therapy of the colitis. Erythema nodosum is the most frequent dermatologic symptom in inflammatory bowel diseases, and it is strongly associated with Crohn disease.[10]
- Hodgkin disease and lymphoma: Erythema nodosum associated with non-Hodgkin lymphoma may precede the diagnosis of lymphoma by months. Reports of erythema nodosum preceding the onset of acute myelogenous leukemia have been published.[11]

- Sarcoidosis: The most common cutaneous manifestation of sarcoidosis is erythema nodosum. A characteristic form of acute sarcoidosis involves the association of erythema nodosum, hilar lymphadenopathy, fever, arthritis, and uveitis, which has been termed Löfgren syndrome. This presentation has a good prognosis, with complete resolution within several months in most patients. HLA-DRB1*03 is associated with Löfgren syndrome. Most DRB1*03-positive patients have resolution of their symptoms within 2 years; however, nearly half of DRB1*03-negative patients have an unremitting course.[12]
- Behçet disease (associated with erythema nodosum)
- Pregnancy: Some patients develop erythema nodosum during pregnancy, most frequently during the second trimester. Repeated episodes occur with subsequent pregnancies or with the use of oral contraceptives.