Peripheral Nervous System Drugs

Cholinergic Drugs

- Muscarinic agonists
- Muscarinic antagonists
- Ganglionic stimulants
- Ganglionic blockers
- Neuromuscular blockers

- Cholinesterase inhibitors: affects all cholinergic receptors

Parasympathetic Actions

Parasympathetic Receptors

Muscarinic Agonists (Parasympathomimetics)

- Limited uses:
  - Urinary retention
  - Increase GI peristalsis
  - Glaucoma, eye surgery
- Adverse effects
  - Bradycardia, hypotension
  - Excess saliva, cramps, diarrhea
  - Urinary (contra: bladder obstruction &surgery)
  - Asthma exacerbation

Muscarinic Poisoning

- Sources
  - Muscarinic agonists
  - Cholinesterase inhibitors
  - Mushrooms
- Symptoms
  - Profuse salivation, tearing, bronchospasm, diarrhea, bradycardia, hypotension
- Treatment: atropine

Muscarinic Antagonists (Parasympatholytics)

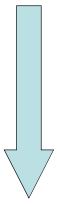
- "Anticholinergics"
- Agents
  - Atropine: strongest, general use
  - Oxybutinin (Ditropan): overactive bladder
  - Tolerodine (Detrol): overactive bladder
  - Scopolamine: sedation, motion sickness
  - Ipratropium: lungs
  - Dicyclomine (Bentyl): IBS, diarrhea
  - Others: ophthalmic procedures, Parkinson's

Atropine

- Mechanism: competitive blockade of muscarinic receptors. High doses will block nicotinic as well
- Pharmacologic effects:
  - Heart: increase heart rate
  - Exocrine Glands: decrease secretions
  - Relaxation of smooth muscle
  - Eye: mydriasis
  - CNS excitation

Atropine

- Dose dependent
  - Low dose



  - High dose
  - Glands: sweat, salivary, bronchial
  - Heart
  - Eye
  - Bladder
  - Intestine motility
  - Lung
  - Stomach

Atropine

- Kinetics: PO, topically (eye), injection
- Therapeutic Uses
  - Preanesthesia
  - Eye surgery
  - Bradycardia
  - Intestinal hypertonicity, hypermotility
  - Muscarinic Agonist Poisoning

Adverse (Anticholinergic) Effects

- Xerostomia (Dry Mouth)
- Blurred vision, photophobia
- Elevation of IOP
- Urinary retention
- Constipation
- Anhidrosis (no sweat)
- Tachycardia
- Asthma: secretions too thick and crusty
- Dementia

Interactions

- Other drugs with anti-muscarinic effects
  - Antihistamines
  - Phenothiazine antipsychotics
  - Tricyclic antidepressants

Anticholinergic Toxicity

- Dry as a bone
- Hot as a hare
- Blind as a bat
- Mad as a hatter
  - **Must determine whether psychosis is real or anticholinergic
- Treatment:
  - Minimize absorption
  - Cholinesterase inhibitor

Cholinesterase Inhibitors

- Reversible
  - Neostigmine: myasthenia gravis
  - Physostigmine: anti-cholinergic antidote
- Irreversible
  - Used as insecticides
  - Developed in WW2 as “nerve gas”
  - One is used for glaucoma

Myasthenia Gravis

- Etiology: Antibodies against Nicotinic-M receptors
- Clinical manifestations: fatigue, muscular weakness, dyspnea
- Treatment
  - Cholinesterase inhibitors
  - Side effects: can cause accumulation of acetylcholine and nicotinic-M and muscarinic receptors

Myasthenia Gravis

- Treatment
  - Side effects cont
  - Muscarinic effects
  - Neuromuscular blockade (toxicity)

Neuromuscular Blockers

- Neuromuscular Blockers
  - Paralytics
  - Repiratory depression, hypotension
  - Agents
    - Nondepolarizing: tubocurarine, et al.
    - Depolarizing: succinylcholine
- Uses
  - Surgery
  - Mechanical Ventilation, ET intubation
  - Adjunct to ECT

Sympathetic Actions

Sympathetic Receptors

Adrenergic Agonists

- Activate alpha and beta receptors
- Catecholamines:
  - Broken down by MAO and COMT in liver and intestine
  - Cannot be given orally, short half-life
  - Epinephrine, Norepinephrine, isoproterenol, dopamine, dobutamine
  - Colorless solutions; color is sign of oxidation

Adrenergic Agonists

- Noncatecholamines
  - Can be given PO
  - Last longer in body
  - Ephedrine, phenylephrine, terbutaline

Receptor Specificity

- Dobutamine: Beta1
- Terbutaline: beta2
- Isoproterenol: beta1 & 2
- Epinephrine: alpha 1 & 2, beta1 & 2

- Relative selectivity
  - Selectivity declines as concentration rises

Alpha1 Stimulation

- Therapeutic effects
  - Vasoconstriction → hemostasis
  - Nasal decongestion
  - Local anesthesia adjunct
  - Increase BP (intensive care, last resort)
  - Mydriasis
- Adverse effects
  - Hypertension
  - Necrosis
  - Bradycardia

Beta1 Activation

- Therapeutic Effects
  - Cardiac arrest
  - Heart Failure
  - Shock
  - A-V heart block
  - Kidney?
- Adverse effects
  - Altered HR, rhythm
  - Angina pectoris

Beta2 activation

- Therapeutic
  - Asthma
  - Preterm labor
- Adverse effects
  - Hyperglycemia
  - Tremor

Epinephrine

- Receptors: all alpha and beta
- Therapeutic uses:
  - Delay absorption of local anesthetics
  - Control superficial bleeding
  - Reduce nasal congestion
  - Raise BP
  - Mydriasis
  - AV block
  - Restart heart in cardiac arrest
  - Asthma
  - Anaphylactic shock

Epinephrine

- Abosrption
  - Inhalation: minimal
  - Injection
- Inactivation: MAO and COMT in liver
- Adverse events
  - Hypertensive crisis
  - Dysrythmias
  - Angina pectoris
  - Necrosis
  - Hyperglycemia

Epinephrine

- Interactoins
  - MAO inhibitors
  - Tricyclic antidepressants
  - Alpha-adrenergic blocking agents
  - Beta-adrenergic blocking agents
- Preparations
  - SC, IM, IV, Intracardiac, intraspinal, inhalation,
  - Lidocaine with epi

Norepinephrine

- Receptor: alpha 1 & 2, beta1
- Therapeutic uses
  - Hypotensive state
  - Cardiac arrest
- Brand: Levophed

Isoprotenerenol

- Receptors: Beta1 and Beta2
- Uses
  - AV block
  - Shock
  - Asthma (no longer used in U.S.)
  - Bronchospasm (2° anesthesia)
- Adverse effects
  - Dysrhythmias, angina pectoris
  - Hyperglycemia

Dopamine

- Receptor: dopamine, alpha1, (beta1 high doses)
- Uses
  - Shock: heart and renal arteries
  - Heart failure
  - ARF: low dose (some studies call effectiveness into question)
- Adverse Effects
  - Dysrhythmias, angina pectoris

Other Adrenergic Agonists

- Dobutamine (beta1): heart failure
- Terbutaline: (beta2):preterm labor, asthma
- Phenylephrine: (alpha1) nasal congestion
- Ephedrine (all alpha and beta):
  - Directly binds & ↑norepinephrine release
  - Nasal congestion
  - Narcolepsy
  - Can be used to make amphetamines

Adrenergic Antagonists

- Can be quite selective for receptors

Alpha1-antagogonists

- Therapeutic uses
  - Hypertension
  - BPH
  - Reverse toxicity of
  - Pheochomocytoma
  - Raynaud's disease
- Adverse effects
  - Orthostatic hypotension
  - Reflex tachycardia
  - Nasal Congestion
  - Inhibition of ejaculation
  - Na+ & H2O retention

Alpha-Adrenergic Blockers

- Prazosin - HTN
- Doxazosin – HTN, BPH
- Terazosin – HTN, BPH
- Tamsulosin – BPH
- Phentolamine – Pheochromocytoma, tissue necrosis

Beta-blockade

- Therapeutic Uses
  - Angina Pectoris
  - HTN
  - Dysrhythmias
  - MI
  - HF
  - Other
    - Hyperthyroid
    - Migraine
    - Stage Fright
    - Pheochromocytoma
    - Glaucoma
- Adverse Effects (β1)
  - Bradycardia
  - ↓CO
  - Precipitate HF
  - AV heart block
  - Rebound cardiac excitation
- Adverse Effects (β2)
  - Bronchoconstriction
  - Inhibition of glycogenolysis

Beta antagonists

- Beta1, Beta2
  - Propanolol
  - Nadolol
  - Pindolol
- Selective
  - Metoprolol
  - Atenolol
  - Bisoprolol
- Beta1,beta2, alpha1
  - Labetalol
  - Carvedilol
- Used for HF
  - Metoprolol
  - Carvedilol

Indirect Adrenergic Antagonists

- Reserpine
  - Suppresses NE synthesis and promotes MAO-mediated destruction
  - Crosses BBB
  - Effects
    - Hypotension
  - Adverse effects
    - Depression, sedation, apathy
    - Bradycardia, hypotension
- Guanethidine: similar but fewer CNS effect

Indirect Adrenergic Antagonists

- Clonidine
  - Causes activation of alpha-2 receptors in CNS
  - Uses
    - Hypertension
    - Pain relief in cancer (epdidural use only)
  - Adverse effects
    - Drowsiness, dry mouth, rebound HTN
  - Preparations
    - Oral: at least twice a day
    - Transdermal: seven days

Indirect Adrenergic Antagonists

- Methyldopa, Methyldopate
  - Similar to clonidine, but are taken up in brain stem neurons and converted to active alpha2 agonist
  - Use: HTN
  - Adverse effects
    - 10 – 20% Positive Coombs test (5%) will go on to have hemolytic anemia
    - Hepatotoxicity
    - Drowsiness, dry mouth, hypotension, etc.