

RSPT 2217  
Critical Care Drugs

## Neuromuscular Blocking Agents

### Neuromuscular Blocking Agents

- Mechanism of Action
  - Prevent acetylcholine stimulation at the motor endplate by combining with and occupying these specific receptors
  - This prevents muscle contraction and induces temporary muscle paralysis
- Two classes of neuromuscular blocking agents
  - Non-depolarizing agents (aka curariform) competitively engage the receptor site in the muscle cell, blocking the action of acetylcholine
  - Depolarizing agents initially instigate muscle contraction, then sustain depolarization time (receptors cannot respond)
    - Further stimulation to the muscle is prevented until the depolarizing effect is terminated

### Neuromuscular Blocking Agents

- Indications
  - As an adjunct to anesthesia to induce skeletal muscle relaxation during surgery
  - During endotracheal intubation
  - Aide in the prevention of laryngospasm
  - Facilitate prolonged mechanical ventilation among patients who otherwise would be difficult to ventilate
- Contraindications
  - Hypersensitivity to the drugs
  - More specific contraindications will be listed with each drug

### Neuromuscular Blocking Agents

- Precautions
  - Respiratory depression and apnea may follow the use of these drugs
    - Intubation with assisted ventilations should be immediately available
  - These agents have no effect on pain threshold or consciousness
    - Use only with adequate anesthesia
  - Use with caution in patients with MG and in patients with cardiovascular, renal, hepatic, pulmonary or endocrine dysfunction
  - Use with extreme caution in patients in which histamine release is a known hazard
    - Have antidotes readily available (neostigmine, edrophonium, pyridostigmine)

### Neuromuscular Blocking Agents

- Adverse Reactions
  - Most frequent: Sustained pharmacologic action of the drug
  - Cardiovascular: Bradycardia, tachycardia, blood pressure changes, arrhythmias, cardiac arrest
  - Pulmonary: respiratory depression, apnea, bronchoconstriction (with histamine release)
  - GI: Excessive salivation
- Overdosage
  - Sustained apnea, cardiovascular collapse, prolonged muscle weakness, release of histamine
  - Treatment consists of ventilatory support and the administration of a cholinergic muscle stimulant

## Neuromuscular Blocking Agents

- Non-depolarizing Agents
  - Atracurium Besylate (Tracrium)
    - May be used to facilitate endotracheal intubation and mechanical ventilation
    - Onset of action  $\leq 3-5$
    - Duration 20-40 min
    - Adverse reactions
      - histamine release
      - hypotension, tachycardia, circulatory collapse
      - erythema, edema
      - bronchospasm
    - Contraindications
      - patients with MG, electrolyte disorders, asthma

## Neuromuscular Blocking Agents

- Non-depolarizing Agents
  - Metocurine Iodide (Metubine)
    - Onset of action  $\leq 2$  min
    - Duration 25-90 min
    - Adverse reactions
      - histamine release
      - hypotension, tachycardia, circulatory collapse
      - erythema, edema
      - bronchospasm
    - Contraindications
      - patients sensitive to iodide

## Neuromuscular Blocking Agents

- Non-depolarizing Agents
  - Pancuronium Bromide (Pavulon)
    - May be used to facilitate endotracheal intubation and mechanical ventilation
    - Onset of action  $<1$  min
    - Duration  $\approx 60$  min
    - Adverse reactions
      - salivation, skin rashes, tachycardia
    - Contraindications
      - patients sensitive to bromide

## Neuromuscular Blocking Agents

- Non-depolarizing Agents
  - Vecuronium Bromide (Norcuron)
    - May be used to facilitate endotracheal intubation and mechanical ventilation
    - Does not cause histamine release and rarely causes cardiovascular side effects
    - Onset of action  $\leq 2.5-3$  min
    - Duration 25-40 min
    - Adverse reactions
      - skeletal muscle weakness
      - respiratory insufficiency, apnea
    - Contraindications
      - patients sensitive to bromide

## Neuromuscular Blocking Agents

- Depolarizing Agents
  - Succinylcholine Chloride (Anectine)
    - used as an adjunct to general anesthesia during surgery and during endotracheal intubation and to reduce the severity of convulsions during electroshock therapy. Not generally used to facilitate mechanical ventilation due to short duration of action.
    - Onset of action 1 min
    - Duration 4-6 min
    - Recovery 8-10 min

## Neuromuscular Blocking Agents

- Depolarizing Agents
  - Succinylcholine Chloride (Anectine)
    - Adverse reactions
      - histamine symptoms
      - bradycardia, tachycardia, blood pressure changes, cardiac arrest, arrhythmias
      - respiratory depression, apnea
    - Contraindications
      - use with caution in patients with renal, liver, cardiovascular, or pulmonary dysfunction
      - relative contraindications include patients with severe burns, tetanus, spinal cord injuries, multiple trauma

## Diuretic Agents

## Diuretic Agents

- Have the ability to facilitate urinary output of water and sodium by enhancing the normal function of the kidneys
  - Achieved through one of three primary mechanisms
    - increasing glomerular filtration rate
    - decreasing sodium reabsorption by the renal tubules
    - excretion of sodium by the kidney
- Classification of diuretic agents is based on their primary mechanism of action

## Diuretic Agents

- Carbonic Anhydrase Inhibitors
  - Generic name - Acetazolamide
  - Brand names - Diamox
  - Actions
    - inhibit the action of carbonic anhydrase, blocking the reabsorption of  $\text{Na}^+$  and  $\text{HCO}_3^-$  from the proximal tubule
    - prevent  $\text{H}^+$  formation and secretion in the renal tubule, which then causes excretion of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{HCO}_3^-$  and  $\text{H}_2\text{O}$ .
  - Indications
    - edema due to CHF
    - drug-induced edema
    - treatment of hyperkalemic periodic paralysis
    - acute mountain sickness after exposure to high altitude

## Diuretic Agents

- Thiazide Diuretics
  - Generic names - chlorothiazide; hydrochlorothiazide
  - Brand names - Diuril; HCTZ
  - Action
    - increases the excretion of  $\text{Na}^+$  and  $\text{Cl}^-$  with a corresponding loss of  $\text{H}_2\text{O}$  by blocking  $\text{Na}^+$  and  $\text{Cl}^-$  reabsorption by the distal renal tubules
  - Indications
    - used in conjunction with other diuretics in pts with edema associated with CHF, pts with hepatic cirrhosis and pts with edema due to renal impairment
    - hypertension; this drug may be used alone or with other hypotensive agents to enhance their effectiveness.

## Diuretic Agents

- Loop Diuretics
  - Generic name - Furosemide
  - Brand names – Lasix
  - Action
    - blocks the reabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$  in the ascending loop of Henle and in the proximal and distal tubules
    - promotes the excretion of  $\text{K}^+$ ,  $\text{Mg}^{++}$ ,  $\text{Ca}^{++}$  and to a lesser extent,  $\text{HCO}_3^-$
  - Indications
    - edema associated with CHF, hepatic cirrhosis, renal disease
    - used as an adjuvant in acute pulmonary edema
    - hypertension (oral route only)

## Diuretic Agents

- Osmotic Diuretics
  - Generic name - Mannitol
  - Brand names - Osmitol
  - Actions
    - block the reabsorption of  $\text{Na}^+$  and  $\text{H}_2\text{O}$  in the proximal tubules, and the descending loop of Henle, increasing the excretion of  $\text{H}_2\text{O}$ ,  $\text{Na}^+$  and  $\text{Cl}^-$
  - Indications
    - treatment or prevention of acute renal failure
    - to decrease intracranial pressure and cerebral edema
    - to decrease intraocular pressure
    - as a diagnostic tool to measure the glomerular filtration rate

## Diuretic Agents

- **K<sup>+</sup> Sparing Diuretics**
  - Generic name – Amiloride, triamterene
  - Brand names - Midamor, Dyrenium; Dyazide (triamterene and hydrochlorothiazide)
  - Actions
    - block Na<sup>+</sup> reabsorption in the distal tubule
    - K<sup>+</sup> is normally exchanged for Na<sup>+</sup> in the distal tubule and then secreted into the urine; by preventing the K<sup>+</sup>/Na<sup>+</sup> exchange, K<sup>+</sup> is spared from secretion
  - Indications
    - essential hypertension
    - hypokalemia
    - management of edema and Na<sup>+</sup> retention in the CHF patient
    - cirrhosis of the liver, when accompanied by edema or ascites

## Anticonvulsant Agents

## Anticonvulsant Agents

- **Actions**
  - Inhibit seizure activity at the motor cortex level
  - Promote the efflux of Na<sup>+</sup> from neurons, thereby stabilizing the threshold against hyperexcitability
- **Generic name Phenytoin Sodium**
- **Brand names Dilantin**
  - Preferred over phenobarbital in the adult, however due to phenytoin's adverse reactions, phenobarbital is the drug of choice in children and infants
  - Phenytoin and phenobarbital are occasionally used together when a single drug is ineffective in controlling seizures

## Anticonvulsant Agents

- **Indications**
  - Control of grand mal and psychomotor seizures
  - Prevention and treatment of seizures occurring during or after neurosurgery
  - Control of status epilepticus of the grand mal type
  - Unlabeled use: antiarrhythmic agent useful in digitalis-induced arrhythmias

## Antiarrhythmic Agents

## Antiarrhythmic Agents

- Antiarrhythmics are divided into four main classes based on their predominant electrophysiological action
  - Class I – Sodium channel blockers
  - Class II – Beta blockers
  - Class III – Potassium channel blockers
  - Class IV – Calcium channel blockers

### Antiarrhythmic Agents

- Class I – Sodium Channel Blockers
  - Depress the fast inward sodium currents in myocardial cells to suppress their automaticity and increase resting potential
  - This class is further divided into 3 levels
    - Class IA
      - actions are related to QT prolongation and may worsen cardiac failure
      - metabolized by the liver and can be monitored with serum concentrations
      - have activity against atrial and ventricular arrhythmias
    - drugs in this class include
      - » disopyramide (Norpace)
      - » procainamide (Procan, Pronestyl)
      - » quinidine

### Antiarrhythmic Agents

- Class I – Sodium Channel Blockers
  - Depress the fast inward sodium currents in myocardial cells to suppress their automaticity and increase resting potential
  - This class is further divided into 3 levels
    - Class IB
      - commonly used and are less likely to have proarrhythmic effects
      - CNS toxicity is common
      - limited to treatment of ventricular arrhythmias
    - drugs in this class include
      - » Lidocaine
      - » Mexiletine (Mexitil)
      - » Tocainide (Tonocard)

### Antiarrhythmic Agents

- Class I – Sodium Channel Blockers
  - Depress the fast inward sodium currents in myocardial cells to suppress their automaticity and increase resting potential
  - This class is further divided into 3 levels
    - Class IC
      - not commonly used and some were removed from the market because of their proarrhythmia side effects
      - indicated for supraventricular arrhythmias, but also have activity against ventricular arrhythmias
    - drugs in this class include
      - » Flecainide (Tambocor)
      - » Propafenone (Rythmol)

### Antiarrhythmic Agents

- Class II – Beta Blockers
  - Inhibit cardiac and pulmonary  $\beta$  receptors, causing bradycardia, decreased contractility and the potential for bronchoconstriction
  - Used to treat hypertension, reduce infarct size in the peri-infarction period, as adjuncts for rate control in atrial fibrillation or flutter and to convert or prevent SVT
  - Actions of beta blocking agents include
    - decreased myocardial contractility
    - prolonged AV conduction time
    - suppressed myocardial automaticity, resulting in decreased heart rate, cardiac output and systemic arterial pressure; all effects are due to a beta-adrenergic blockade on the cardiac beta receptors

### Antiarrhythmic Agents

- Class II – Beta Blockers
  - Drugs in this class include
    - Acebutolol (Sectral)
    - Atenolol (Tenormin)
    - Esmolol (Brevibloc)
    - Metoprolol (Lopressor)
    - Nadolol (Visken)
    - Propranolol (Inderal)

### Antiarrhythmic Agents

- Class III – Potassium Channel Blockers
  - Class III agents are effective for both supraventricular and ventricular arrhythmias
  - Drugs in this class include:
    - Amiodarone (Cordarone, Pacerone)
    - Dofetilide (Tikosyn)
    - Ibutilide (Corert)

### Antiarrhythmic Agents

- Class IV – Calcium Channel Blockers
  - Three major types are available
    - dihydropyridines, which do not slow the heart rate or cause other abnormal heart rates or rhythms (cardiac arrhythmias)
  - Examples include
    - amlodipine (Norvasc)
    - sustained release nifedipine (Procardia XL, Adalat CC)
    - felodipine (Plendil)
    - nisoldipine (Sular)
    - clevidipine (Cleviprex)
    - nicardipine (Cardene)

### Antiarrhythmic Agents

- Class IV – Calcium Channel Blockers
  - The other two types of calcium channel blockers are referred to as the non-dihydropyridine agents
    - verapamil (Calan, Covera, Isoptin, Verelan)
    - diltiazem (Cardizem, Tiazac, Dilacor, and Diltia).

### Antiarrhythmic Agents

- Other Antiarrhythmics
  - Adenosine (Adenocard)
    - an endogenous nucleoside occurring in all cells of the body
    - slows conduction time through the A-V node
    - can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardia (PSVT)
  - Digoxin (Lanoxin)
    - increases the strength and vigor of heart contractions
    - used to treatment of heart failure
    - increases the force of contraction of the muscle of the heart by inhibiting the activity of ATPase which increases calcium in heart muscle and therefore increases the force of heart contractions

### Antianginal Agents

### Antianginal Agents

- Actions
  - Relax and dilate vascular smooth muscle of both arterial and venous vessels
  - Improves coronary circulating blood flow
  - decreases myocardial O<sub>2</sub> consumption
  - decreases systemic and peripheral vascular resistance and arterial pressure
  - decreases elevated CVP, PCWP and pulmonary vascular resistance

### Antianginal Agents

- Indications
  - IV: control and prevention of hypertensive episodes due to surgery, cardiovascular procedures and CAB; CHF associated with acute MI
  - Sublingual: relief of acute angina; to decrease myocardial work in pts with acute MI or CHF
- Drugs in this class include
  - Nitroglycerin (Tridel, Nitrostat, Nitrobid)

## Vasopressors and Inotropes

## Vasopressors and Inotropes

- Indications
  - Sympathomimetic agents used in shock to treat hypoperfusion and provide hemodynamic support
- Action
  - Increase myocardial contractility, constrict capacitance vessels and dilate resistance vessels
- Drugs in this group include
  - norepinephrine (Levophed)
  - epinephrine (Adrenaline)
  - dopamine (Intropin)
  - isoproterenol (Isuprel)
  - Phenylephrine (Neo-Synephrine)
  - Vasopressin (Pitressin)
  - dobutamine (Dobutrex)

## Antihypertensive Agents

## Antihypertensive Agents

- Arterial blood pressure
  - Determined by blood flow and the resistance to blood flow
  - Highest during cardiac systole; lowest at the end of diastole
  - Hypertension (HTN) can damage the heart, brain, kidney and eye
  - Referred to as cardiovascular disease (CVD)
    - uncontrolled HTN increases CVD morbidity and mortality due to increased risk of left ventricular hypertrophy, angina, MI, cardiac failure, stroke, PAD, retinopathy, and renal failure
- Blood pressure values are categorized according to the following table

Category	Systolic (mmHg)	Diastolic(mmHg)
Optimal	<120	<80
Normal	<130	<85
High normal	130-139	85-89
Stage 1 HTN	140-159	90-99
Stage 2 HTN	160-179	100-109
Stage 3 HTN	≥180	≥110

## Antihypertensive Agents

- Uncomplicated HTN
  - Stages 1 & 2 HTN = uncomplicated, non-emergency HTN
  - First-line agents are thiazide diuretics and  $\beta$ -blockers because they are proven to reduce morbidity and mortality
  - Alternative first-line agents include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II-receptor blockers (ARBs), and calcium antagonists
  - Vasodilators,  $\alpha$ -blocking agents,  $\alpha_2$  agonists and antiadrenergic agents are considered second-line antihypertensives

### Antihypertensive Agents

- HTN Crisis
  - Stage 3 HTN is considered a hypertensive crisis
  - Represents either a hypertensive urgency (diastolic pressure of >120 mmHg without signs or symptoms of target organ complications) or a hypertensive emergency (elevated diastolic pressure accompanied by acute or chronic target organ injury)
  - Treatment of HTN urgency and the reduction in blood pressure may span several hours or days
- HTN emergencies
  - can lead to intracranial hemorrhage, severe retinopathy, renal failure, unstable angina, acute left ventricular failure or dissecting aortic aneurysm
  - require invasive arterial blood pressure monitoring and immediate blood pressure reduction with parenteral hypertensives

### Antihypertensive Agents

- HTN Crisis
  - HTN urgency is treated with  $\beta$ -blockers and angiotensin-converting enzyme inhibitors (ACEIs)
  - HTN emergencies are treated with IV agents such as labetalol, nitroprusside and diazoxide are routinely used to manage these emergencies

### Antihypertensive Agents

- Angiotension-Converting Enzyme Inhibitors (ACEI)
  - When there is a reduction in renal blood flow, rennin is released into the circulation, where it acts on angiotensionogen to produce angiotensin I
  - In the pulmonary vasculature, angiotensin I is then converted by angiotensin-converting-enzyme (ACE) to angiotensin II, a very potent endogenous vasoconstrictor
  - ACEIs block the conversion of angiotensin I to angiotensin II
  - ACEIs are indicated for hypertension, heart failure and systolic dysfunction, secondary prevention of MI, left ventricular dysfunction and diabetic nephropathy

### Antihypertensive Agents

- Angiotension-Converting Enzyme Inhibitors
  - Nine ACEIs are available in the U.S.
    - Benazepril (Lotensin)
    - Fosinopril (Monopril)
    - Quinapril (Accupril)
    - Captopril (Capoten)
    - Lisinopril (Prinivil, Zestril)
    - Ramipril (Altace)
    - Enalapril (Vasotec)
    - Moexipril (Univasc)
    - Trandolapril (Mavik)

### Antihypertensive Agents

- Angiotension II-Receptor Blockers (ARB)
  - Several non-renin and non-ACE pathways are used to produce angiotensin II
  - ACEIs do not completely block the synthesis of angiotensin II
  - ARBs are angiotension II type 1 ( $AT_1$ ) receptor antagonists
    - $AT_1$  receptors are found in many tissues such as the vascular smooth muscle, myocardial tissue, brain, kidney, liver, uterus, and adrenal glands
    - The six ARBs available in the U.S. are:

### Antihypertensive Agents

- Angiotension II-Receptor Blockers (ARB)
  - Six ARBs are available in the U.S.
    - Losartan (Cozaar)
    - Irbesartan (Avapro)
    - Valsartan (Diovan)
    - Candesartan (Atacand)
    - Telmisartan (Micardis)
    - Eprosartan (Teveten)



### Antihypertensive Agents

- Calcium Channel Blockers
  - Vascular smooth muscle and cardiac cell contraction is dependent on the free intracellular calcium concentration
  - Calcium from the extracellular fluid enters either the high-voltage-gated L-type calcium channels or the low-voltage-gated T-type calcium channels
    - L-channel blockade mediates coronary and peripheral vasodilation and may also cause reflex sympathetic activation or a negative inotropic effect
    - T-channel blockade mediates coronary and peripheral vasodilation but does not cause reflex sympathetic activation
  - Conventional calcium channel blockers inhibit only L-channels

### Antihypertensive Agents

- Calcium Channel Blockers
  - Verapamil and to a lesser extent diltiazem lower SA node automaticity and decrease AV node conduction and are indicated for the treatment of hypertension, angina and dysrhythmias

### Antihypertensive Agents

- Calcium Channel Blockers
  - Drugs in this class include
    - Verapamil (Calan)
    - Bepridil (Vasor)
    - Nicardipine (Cardene)
    - Diltiazem (Cardizem)
    - Felodipine (Plendil)
    - Nifedipine (Procardia)
    - Amlodipine (Norvasc)
    - Isradipine (DynaCirc)
    - Nisoldipine (Sular)

### Antihypertensive Agents

- $\beta$  Adrenergic Blocking Agents
  - The antihypertensive effects of  $\beta$  blockers are multimechanistic
    - Blockade of  $\beta$  receptors on the renal juxtaglomerular cells, leading to rennin blockade and decreased angiotensin II concentrations
    - Blockade of myocardial  $\beta$  receptors, leading to decreased cardiac contractility and heart rate, diminishing C.O.
    - Blockade of CNS  $\beta$  receptors, leading to decreased sympathetic output from the CNS and blockade of peripheral  $\beta$  receptors, decreasing norepinephrine concentrations
  - $\beta$  blockers are indicated for essential hypertension, angina pectoris, cardiac dysrhythmias, 2° prevention of MI, CHF and pheochromocytoma
  - Possible  $\beta$  blocker-induced pulmonary dysfunction includes bronchospasm, bronchial obstruction, rales, wheezing, dyspnea, cough and exacerbation of stable asthma or COPD

### Antihypertensive Agents

- $\beta$  Adrenergic Blocking Agents
  - Drugs in this class include
    - Acebutolol (Sectral)
    - Atenolol (Tenormin)
    - Betaxolol (Kerlone)
    - Labetalol (Normodyne)
    - Metoprolol (Lopressor)
    - Nadolol (Visken)
    - Propranolol (Inderal)

### Antithrombotic Agents

### Antithrombotic Agents

- Three categories of antithrombotic agents are available
  - Anticoagulant
    - Prevent the formation of the fibrin clot and prevent further clot formation in already existing thrombi. Agents in this category include:
    - Indicated for the prophylaxis and treatment of
      - venous thromboembolism and pulmonary embolism
      - treatment of atrial fib with embolization
      - diagnosis and treatment of disseminated intravascular coagulation
      - prophylaxis and treatment of peripheral arterial embolism

### Antithrombotic Agents

- Three categories of antithrombotic agents are available
  - Anticoagulant
    - Drugs in this class include
      - Heparin
      - Warfarin (Coumadin)
      - Enoxaparin (Lovenox)
      - Dalteparin (Fragmin)
      - Danaparoid (Orgaran)
      - Ardeparin (Normiflo)
      - Tinzaparin (Innohep)
      - Lepirudin (Refludan)
      - Anisindione (Miradon)

### Antithrombotic Agents

- Three categories of antithrombotic agents are available
  - Antiplatelet
    - Inhibit the action of platelets in the clotting process
    - Drugs in this class include
      - Aspirin
      - Dipyridamole (Persantine)
      - Aspirin and dipyridamole (Aggrenox)
      - Ticlopidine (Ticlid)
      - Clopidogrel (Plavix)
      - Cilostazol (Pletal)
      - Abciximab (ReoPro)
      - Tirofiban (Aggrastat)
      - Eptifibatide (Integrilin)

### Antithrombotic Agents

- Three categories of antithrombotic agents are available
  - Thrombolytic
    - Indicated for the management of ST-segment-elevation acute MI
    - Reduce the incidence of heart failure and death associated with an acute MI
    - Restore coronary blood flow by dissolving the thrombus, thus limiting the extent of ischemia and necrosis
    - Patients should receive thrombolytic therapy within 12 hours of symptom onset
    - Most common side effects
      - minor bleeding (superficial and surface bleeding)
      - major bleeding (gastrointestinal, genitourinary, respiratory tract, retroperitoneal and intracranial hemorrhage)

### Antithrombotic Agents

- Three categories of antithrombotic agents are available
  - Thrombolytic
    - Drugs in this class include
      - Alteplase (Activase)
      - Reteplase (Retavase)
      - Urokinase (Abbokinase)
      - Streptokinase (Streptase)
      - Anistreplase (Eminase)
      - Tenecteplase (TNKase)