RSPT 2317
Critical Care Drugs

NEUROMUSCULAR BLOCKING AGENTS

Mechanism of Action:
Neuromuscular blocking agents prevent acetylcholine stimulation at the motor endplate by combining with and occupying these specific receptors. Through this action, neuromuscular blocking agents prevent muscle contraction and induce temporary muscle immobility (paralysis).

There are two classes of neuromuscular blocking agents: nondepolarizing and depolarizing. Nondepolarizing agents competitively engage the receptor site in the muscle cell, blocking the action of acetylcholine. These are also called curariform since they resemble curare. Depolarizing agents initially instigate muscle contraction (mimicking acetylcholine), then sustain depolarization time (receptors cannot respond to acetylcholine while in a depolarized mode). Any further stimulation to the muscle is prevented until the depolarizing agent's effect is terminated. Only when the effect wears off or is hydrolyzed by pseudocholinesterase is the depolarized receptor allowed to return to its normal state of activities.

Indications for Use:
These agents are indicated for use as an adjunct to anesthesia to induce skeletal muscle relaxation during surgery, during endotracheal intubation and as an aide in the prevention of laryngospasm. Neuromuscular blocking agents are also used as an aide to electroshock therapy to prevent muscle spasms and fractures and may be used to reduce the severity of convulsions. Nondepolarizing agents are also used to facilitate prolonged mechanical ventilation among patients who otherwise would be difficult to ventilate.

Contraindications for Use:
Hypersensitivity to these drugs. Other, more specific contraindications will be listed with each drug.

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

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.

Nondepolarizing Neuromuscular Blocking Agents

Generic name:	Atracurium Besylate
Brand names:	Tracrium
Mode of Action:	Competitively engages the neuromuscular receptor site, antagonizing the effects of acetylcholine at the motor endplate. May cause release of histamine.
Onset of action:	≤ 3-5 min after injection
Duration:	20-40 min
Dosage form:	***IV solution:*** 10 mg/ml in 5 and 10 ml vials
Adverse reactions:	Histamine release symptoms; hypotension, erythema, tachycardia, circulatory collapse, edema, bronchospasm
Contraindications:	Patients with MG, electrolyte disorders, bronchial asthma

Generic name:	Metocurine Iodide
Brand names:	Metubine
Mode of Action:	Competitively engages the neuromuscular receptor site, antagonizing the effects of acetylcholine at the motor endplate. May cause release of histamine. Twice as potent as curare with fewer circulatory system side effects.
Onset of action:	≤ 2 min
Duration:	25-90 min
Dosage form:	***IV solution:*** 2 mg/ml in 20 ml vials
Adverse reactions:	Allergic reaction to drug or iodide. Histamine release symptoms; hypotension, erythema, tachycardia, circulatory collapse, edema, bronchospasm
Contraindications:	Patients sensitive to iodide

Generic name:	Pancuronium Bromide
Brand names:	Pavulon
Mode of Action:	Similar to curare; however pancuronium is 5 times as potent and rarely causes histamine release and does not cause hypotension. Pancuronium may be used to facilitate endotracheal intubation and mechanical ventilation.
Onset of action:	<1 min
Duration:	60 min
Dosage form:	***IV solution:*** 1 mg/ml in 10 ml vials and 2 mg/ml in 2 and 5 ml vials and syringes
Adverse reactions:	Salivation, skin rashes, tachycardia
Contraindications:	Patients sensitive to bromide

Generic name:	Tubocurarine (Curare)
Mode of Action:	Produces a nondepolarizing blockade at the neuromuscular junction. Causes paralysis of all skeletal muscles. Cumulative effects may occur. Has a low therapeutic index. Causes histamine release.
Onset of action:	<2 min
Duration:	25-90 min
Dosage form:	***IV solution:*** 3 mg/ml in 10 and 20 ml vials and 5 ml syringes
Adverse reactions:	Hypotension due to ganglionic blocking; bronchospasm and all other symptoms due to histamine release
Contraindications:	Use with extreme caution in patients with renal, liver, circulatory, or pulmonary dysfunction.

Generic name:	Vecuronium Bromide
Brand names:	Norcuron
Mode of Action:	Similar pancuronium; slightly more potent and 4 times more potent than atracurium. Does not cause histamine release and rarely causes cardiovascular side effects.
Onset of action:	≤ 2.5-3 min
Duration:	25-40 min
Dosage form:	***IV solution:*** 10 mg powder in 5 and 10 ml vials with diluent
Adverse reactions:	Skeletal muscle weakness, respiratory insufficiency, apnea
Contraindications:	Patients sensitive to bromide

Depolarizing Neuromuscular Blocking Agents

Generic name:	Succinylcholine Chloride
Brand names:	Anectine, Quelicin
Mode of Action:	Depolarizing neuromuscular blocking agent that combines with the receptors of the motor endplate. Succinylcholine's effect initially excites skeletal muscle; then sustains the depolarization time at these receptors, preventing acetylcholine receptor stimulation. Succinylcholine is 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
Dosage form:	***IV, IM solution:*** 20 mg/ml in 10 ml vials, 50 mg/ml in 10 ml amps, 100 mg powder in 5 ml vial with diluent
Adverse reactions:	Histamine induced symptoms, along with 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

These agents have the ability to facilitate urinary output of water and sodium by enhancing the normal function of the kidneys. This is done by one of three primary mechanisms:

1. ↑ the glomerular filtration rate.
2. ↓ sodium reabsorption by the renal tubules.
3. Induce and promote the excretion of sodium by the kidney.

Classification of diuretic agents is based on their primary mechanism of action.

Carbonic Anhydrase Inhibitors

Action:	Inhibit the action of carbonic anhydrase, blocking the reabsorption of Na^+ and HCO_3^- from the proximal tubule. This prevents H^+ formation and secretion in the renal tubule, which then causes ↑excretion of Na^+, K^+, HCO_3^- and H_2O.
Indications:	• Edema due to CHF • Drug-induced edema • Treatment of hyperkalemic periodic paralysis • Acute mountain sickness after exposure to high altitude

Generic names: Acetazolamide
Brand names: Diamox

Thiazide Diuretics

Actions: ↑ the excretion of Na^+ and Cl^- with a corresponding loss of H_2O by blocking Na^+ and 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 agent to enhance their effectiveness.

Generic names: Chlorothiazide; hydrochlorothiazide; metolazone
Brand names: Diuril; HydroDIURIL; Zaroxolyn

Loop Diuretics

Actions: Block the reabsorption of Na^+ and Cl^- in the ascending loop of Henle and in the proximal and distal tubules; promotes the excretion of K^+, Mg^{++}, Ca^{++} and to a lesser extent, HCO_3^-.

Indications:
- Edema associated with CHF, hepatic cirrhosis, renal disease
- Used as an adjuvant in acute pulmonary edema
- Hypertension (oral route only)

Generic names: Furosemide, torsemide
Brand names: Lasix; Demadex

Osmotic Diuretics

Actions: Block the reabsorption of Na^+ and H_2O in the proximal tubules, and the descending loop of Henle. The excretion not only of H_2O, but also of Na^+ and Cl^-, is ↑.

Indications:
- Treatment or prevention of acute renal failure
- ↓ intracranial pressure and cerebral edema
- ↓ intraocular pressure
- As a diagnostic tool to measure the glomerular filtration rate.

Generic name: Mannitol
Brand names: Osmitrol

K^+ Sparing Diuretics

Actions: Block Na^+ reabsorption in the distal tubule. K^+ is normally exchanged for Na^+ in the distal tubule and then secreted into the urine. By preventing the K^+- Na^+ exchange, K^+ is spared from secretion.

Indications:
- Essential hypertension
- Hypokalemia
- Management of edema and Na^+ retention in the CHF patient
- Cirrhosis of the liver, when accompanied by edema or ascites

Generic name: Amiloride: triamterene
Brand names: Midamor, Dyrenium; Dyazide (triamterene and hydrochlorothiazide)

ANTICONVULSANT AGENTS

Actions: Inhibits seizure activity at the motor cortex level. Promotes the efflux of Na^+ from neurons, thereby stabilizing the threshold against hyperexcitability. 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.

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

Generic name: Phenytoin Sodium
Brand names: Dilantin

CARDIOVASCULAR AGENTS

Antiarrhythmic Agents

Antiarrhythmics are divided into four classes based on their predominant electrophysiological action. The Singh–Vaughn Williams classification scheme is most often used, but several agents possess activity from more than one class.

Class I Antiarrhythmic Agents

These agents act by depressing 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 – The actions of these agents are related to QT prolongation and may worsen cardiac failure. Drugs in this class are metabolized by the liver and can be monitored with serum concentrations. They have activity against atrial and ventricular arrhythmias. Drugs in this class include:

Disopyramide (Norpace) Procainamide (Pronestyl) Quinidine

Class IB – These agents are also commonly used and are less likely to have proarrhythmic effects. CNS toxicity is common. Class IB agents are limited to treatment of ventricular arrhythmias. Drugs in this class include:

Lidocaine Tocainide (Tonocard)
Mexiletine (Mexitil) Phenytoin (Dilantin)

Class IC – These agents are not commonly used and some were removed from the market because of their proarrhythmia side effects. When used, these agents are indicated for supraventricular arrhythmias, but also have activity against ventricular arrhythmias. Drugs in this class include:

Flecainide (Tambocar) Encainide (Tambocor) Propafenone (Rythmol)

Class II Antiarrhythmic Agents

Class II includes the β-blocking agents. These agents are used for the treatment of hypertension, for reduction of infarct size in the periinfarction period, as adjuncts for rate control in atrial

fibrillation or flutter and to convert or prevent SVT. The intravenous agents may be used to treat arrhythmias acutely. Actions of β-adrenergic blocking agents include ↓ myocardial contractility, prolonged AV conduction time, suppressed myocardial automaticity, resulting in ↓ heart rate, ↓ cardiac output and ↓ systemic arterial pressure; all effects are due to a β-adrenergic blockade on the cardiac β receptors. Drugs in this class include:

Acebutolol (Sectral)	Labetalol (Normodyne)	Propranolol (Inderal)
Atenolol (Tenormin)	Metoprolol (Lopressor)	
Esmolol (Brevibloc)	Nadolol (Visken)	

Class III Antiarrhythmic Agents

Class III agents are effective for both supraventricular and ventricular arrhythmias. Drugs in this class include:

Amiodarone (Cordarone)	Ibutilide (Corvert)
Dofetilide (Tikosyn)	Sotalol (Betapace)

Class IV Antiarrhythmic Agents

Calcium channel blockers are commonly used for the treatment of hypertension, but two of the drugs in this class are also used for the acute treatment of supraventricular arrhythmias and long-term control of ventricular rate in atrial fibrillation or flutter. Both share the potential for hypotension and worsening of CHF and both are metabolized by the liver. As a result, these agents should be used with caution in patients with poor cardiac function or renal dysfunction. These agents are:

Diltiazem (Cardizem) Verapamil (Calan, Isoptin, Verelan)

Other Antiarrhythmic Agents

Adenosine (Adenocard) Digoxoin (Lanoxin)

Antianginal Agents

Angina pectoris is a symptom of myocardial ischemia. Ischemia is defined as a lack of oxgen and decreased or no blood flow to the myocardium. The most common antianginal agents, the nitrates relax and dilate vascular smooth muscle of both arterial and venous vessels; improve coronary circulating blood flow, ↓ myocardial O_2 consumption and ↓ systemic and peripheral vascular resistance and arterial pressure; ↓ elevated CVP, PCWP and pulmonary vascular resistance. Drugs in this category include:

Nitroglycerin (Tridel, Nitrostat, Nitrobid) Isosorbide dinitrate (Isordil) Isosorbide mononitrate (Imdur)

Vasopressors and Inotropes

Vasopressors and inotropes are sympathomimetic agents used in shock to treat hypoperfusion and provide hemodynamic support. Vasopressors and inotropes increase myocardial contractility, constrict capacitance vessels and dilate resistance vessels. The agents routinely used for hemodynamic support and are dopamine (Intropin), dobutamine (Dobutrex), norepinephrine, and to a lesser extent, epinephrine.

Antihypertensive Agents

Arterial blood pressure is generated by the interplay between the blood flow and the resistance to blood flow, Arterial blood pressure reaches a peak during cardiac systole and a nadir at the end of diastole. High blood pressure (hypertension) adversely affects numerous body organs, including the heart, brain, kidney and eye. Damage to these organ systems resulting from hypertension is termed cardiovascular disease (CVD). Uncontrolled hypertension 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
Hypertension		
Stage 1	140-159	90-99
Stage 2	160-179	100-109
Stage 3	≥180	≥110

A patient with Stage 3 hypertension (severe hypertension) is considered to be in a hypertensive crisis. 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). Oral captopril (Capoten), clonidine (Catapres) and labetolol (Normodyne) are routinely used to treat hypertensive urgency and the reduction in blood pressure may span several hours or days. Hypertensive emergencies, which may 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. IV labetolol (Normodyne), nitroprusside (Nitropress) and diazoxide (Hyperstat) are routinely used to manage these emergencies.

A variety of agents is available for the treatment of uncomplicated, non-emergency hypertension. First-line agents are thiazide diuretics (described previous) and β-blockers (see *Class II Antiarrhythmic Agents*) 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 (see *Class IV Antiarrhythmic Agents*). Vasodilators, α-blocking agents, α_2 agonists and antiadrenergic agents are considered second-line antihypertensives.

Angiotension-Converting Enzyme Inhibitors

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. Angiotensin II is 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. The nine ACEIs available in the U.S. are:

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

Angiotension II-Receptor Blockers
Several non-renin and non-ACE pathways are used to produce angiotensin II. Therefor, ACEI do not completely block the synthesis of angiotensin II. ARBs are angiotension II type 1 (AT_1) receptor atagonists. 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:

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

Calcium Antagonists (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 channesl or the low-voltage-gated T-type calcium channels. L-channel blockade mediates coronary and perpheral 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. Verapamil and to a lesser extent diltiazem lower SA node automaticity and decrease AV node conduction. As a result, these agents are indicated for the treatment of hypertension, angina and dysrrhythmias. Drugs in this class include:

Verapamil (Calan)	Bepridil (Vascor)	Nicardipine (Cardene)
Diltiazem (Cardizem)	Felodipine (Plendil)	Nifedipine (Procardia)
Amlodipine (Norvasc)	Isradipine (DynaCirc)	Nisoldipine (Sular)

β-Adrenergic Blocking Agents

The antihypertensive effects of β blockers are multimechanistic:
- Blockade of β receptors on the renal juxtaglomerular cells, leading to rennin blockade and decreased angiotensin II concentrations
- Blockade of myocardial β recptors, leading to decreased cardiac contractility and heart rate, diminishing C.O.
- Blockade of CNS β receptors, leading to decreased sympathetic output from the CNS and blockade of peripheral β receptors, decreasing norepinephrine concentrations

β blockers are indicated for essential hypertesion, angina pectoris, cardiac dysrrhythmias, 2° prevention of MI, CHF and pheochromocytoma. Possible β blocker-induced pulmonary dysfunction includes bronchospasm, bronchial obstruction, rales, wheezing, dyspnea, cough and exacerbation of stable asthma or COPD. Drugs in this class include:

Acebutolol (Sectral)	Labetalol (Normodyne)	Propranolol (Inderal)
Atenolol (Tenormin)	Metoprolol (Lopressor)	
Betaxlol (Kerlone)	Nadolol (Visken)	

Antithrombotic Agents

Three categories of antithrombotic agents are available:
- Anticoagulant – these agents work by preventing the formation of the fibrin clot and preventing the further clot formation in already existing thrombi. Agents in this category include:
    - Heparin – 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, and prophylaxis and treatment of peripheral arterial embolism.

  - Warfarin (Coumadin) – indicated for the prophylaxis and treatment of venous thrombosis, pulmonary embolism and thromboembolic complications associated with atrial fib and cardiac valve replacement and as an adjunct in the treatment of coronary occlusion. Usually administered following an initial course of heparin.
  - Enoxaparin (Lovenox)
  - Dalteparin (Fragmin)
  - Danaparoid (Orgaran)
  - Ardeparin (Normiflo)
  - Tinzaparin (Innohep)
  - Lepirudin (Refludan)
  - Anisindione (Miradon)
- Antiplatelet – these agents inhibit the action of platelets in the clotting process. Agents in this category include:
  - Aspirin – prostaglandin inhibitor
  - Dipyridamole (Persantine) – vasodilator; platelet adhesion inhibitor
  - Aspirin and dipyridamole (Aggrenox) – indicated in pts. with TIAs or Hx of stroke
  - Ticlopidine (Ticlid) – platelet aggregation inhibitor
  - Clopidogrel (Plavix) – platelet aggregation inhibitor
  - Cilostazol (Pletal) – indicated for pts. with intermittent claudication; ***contraindicated*** in pts. with heart failure and CAD
  - Abciximab (ReoPro) – glycoprotein IIb/IIIa inhibitor*
  - Tirofiban (Aggrastat) – glycoprotein IIb/IIIa inhibitor*
  - Eptifibatide (Integrilin) – glycoprotein IIb/IIIa inhibitor*

    **GP IIb/IIIa inhibitors are indicated for the treatment of patients with acute coronary syndromes – unstable aginia or non-ST-elevation acute MI, including patients who are medically managed and those undergoing percutaneous coronary intervention.*
- Thrombolytic – these agents are indicated for the management of ST-segment-elevation acute MI. Thrombolytics reduce the incidence of of heart failure and death associated with an acute MI. Thrombolytics restore coronary blood flow by dissolving the thrombus, thus limiting the extent of ischemia and necrosis. Eligible patients should receive thrombolytic therapy within 12 hours of of symptom onset. The most common side effect of these agents is minor bleeding (superficial and surface bleeding) and major bleeding (gastrointestinal, genitourinary, respiratory tract, retroperitoneal and intracranial hemorrhage). Agents in this category include:
  - Alteplase (Activase)
  - Reteplase (Retavase)
  - Urokinase (Abbokinase)
  - Streptokinase (Streptase)
  - Anistreplase (Eminase)
  - Tenecteplase (TNKase)