

Advanced Pharmacology

Gina St. Jean RN, MSN, CCRN-CSC
Clinical Nurse Educator
HVCC & PCU

Objectives

- Identify the basic concepts and terminology of pharmacology
- Identify the process of drug metabolism and factors that influence it
- Identify the major categories of drugs utilized most in intermediate care
- Review the most predominantly used medications in intermediate care
- Knowledge of how the major categories of drugs used in intermediate care work and how to safely administer them.



Terminology

- Pharmacology The study of drugs, their sources, their nature, and their properties. Pharmacology is the study of the body's reaction to drugs.
- Adverse Reaction An undesirable response to a drug that may be either sudden or take days to occur.
- Allergy A reaction to a medication that causes local and systemic symptoms (wheezing, watery eyes, swelling, itching, rash, etc.).
- Anaphylactic Reaction The most severe allergic reaction which involves cardiovascular collapse (hypotension, airway swelling, and altered mental status)
- Tachyphylaxis An acute decrease in the response to a drug after its administration. This can sometimes be caused by depletion or marked reduction of the amount of neurotransmitter responsible for creating the drug's effect, or by the depletion of receptors available to which the drug or neurotransmitter can bind. This depletion is caused by the cells reducing the number of receptors in response to their saturation.

Med Administration Safety

- **5 Rights! Don't skip this!**
- High Alert Medications
- Tall Man lettering
- Second RN witnessing
- Bar Code Scanning
- Smart Pumps
- Premixed medications
- “Do Not Disturb” Med pass notifications

Half Life

- The amount of time that a drug remains at a therapeutic level to continue to produce the desired effect and the time it takes the body to metabolize the drug's concentration by 50%. Very important for planning repeated doses. It generally takes about 5 times longer than the half-life for a drug to reach a “steady state” in the blood plasma. Hence, after 5 half-lives a drug is considered cleared from the system.

Steady State

- The rate of drug intake equals the rate of drug elimination.¹
- The time required to reach steady state depends on the elimination half-life of the drug, defined as the time required for the serum drug concentration to decrease by 50%.
- The half-life is itself determined by the metabolism and excretion rates of the drug. In the absence of a loading dose, at least 5 half-lives are usually required to achieve a steady state.
- Except in medical emergencies, the monitored drug should be allowed to reach a new steady state following a dosage change and the addition or discontinuation of a co-administered drug.¹ Similarly, the same amount of time needs to elapse to almost completely eliminate a discontinued drug that had reached steady state.

First Pass Metabolism

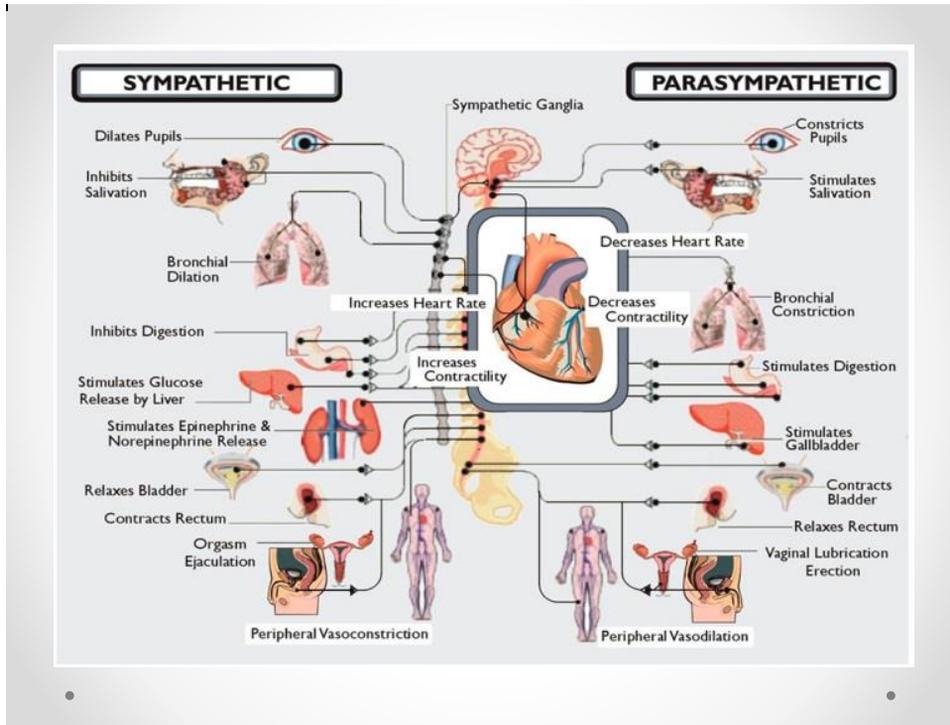
- A process in which a drug administered by mouth is absorbed from the gastrointestinal tract and transported via the portal vein to the liver, where it is metabolized. As a result, in some cases only a small proportion of the active drug reaches the systemic circulation and its intended target tissue. First-pass metabolism can be bypassed by giving the drug via sublingual or buccal routes.

Cytochrome P450

- The CYP450 enzymes are essential for the production of numerous agents including cholesterol and steroids. Additionally, these enzymes are necessary for the detoxification of foreign chemicals and the metabolism of drugs.
- There are more than 50 CYP450 enzymes

Adrenoceptors

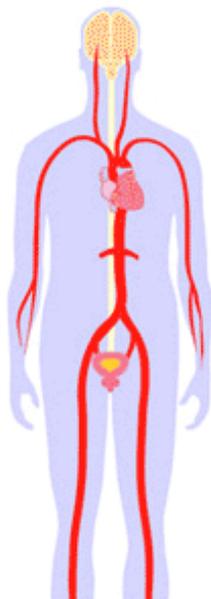
- Adrenoceptors interact with sympathomimetic agents
- The physiological response to adrenoceptor stimulation depends on the location of the receptors.
- Receptors are protein molecules usually found embedded within surface of a cell that receives chemical signals from outside the cell. When such chemical signals bind to a receptor, they cause some form of cellular/tissue response.
- Agonists activate receptors to produce the desired response.
- Antagonists prevent receptor activation.



Medscape

www.medscape.com

α_1 and β_1 Adrenoceptors



α_1

Located in smooth muscle cell membrane and promotes contraction of the smooth muscle of peripheral blood vessels, bladder neck, prostate capsule, and prostate fibromuscular stroma.

β_1

Located in cardiac muscle cell membrane and stimulates heart rate and myocardial contractility.

WebMD/ Medscape

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Types of Adrenoreceptors

- **Alpha 1**- vasoconstriction of most blood vessels
- **Alpha 2**- Inhibits norepinephrine release and inhibits insulin release
- **Beta 1**- Increases CO₂, increases HR, Increases force of contraction.
- **Beta 2**- Increases hepatic glucose output, bronchodilation, and skeletal muscle dilation

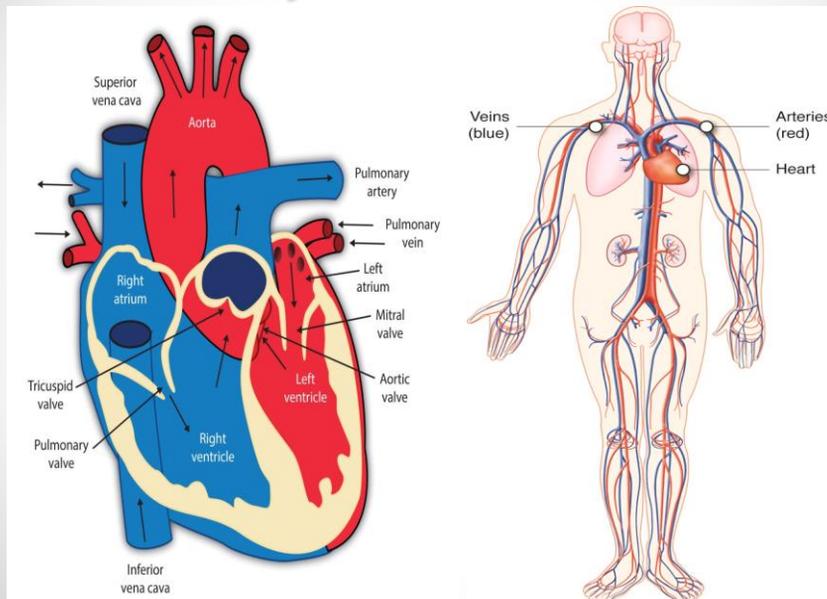
Catecholamines

- Each person has two adrenal glands; one located on top of each of the body's two kidneys. These glands are important to the body's endocrine (hormonal) system. Each adrenal gland has two main parts that function separately:
 - **Adrenal cortex.** The outer part of the adrenal gland is called the cortex. The adrenal cortex makes three main hormones: cortisol, aldosterone, and dehydroepiandrosterone (DHEA). These hormones carefully control metabolism and body characteristics, such as hair growth and body shape.
 - **Adrenal medulla.** The gland's inner part is called the medulla. The adrenal medulla makes three other hormones: epinephrine, norepinephrine, and dopamine. These hormones control the body's responses to stress, including the "fight or flight" adrenaline surge.
- These hormones are considered catecholamines and they mediate the cardiovascular system's response to external stressors by stimulating one or more of the receptors.
- The stimulation of these receptors is largely controlled by calcium channels in the body. The balance of sodium, calcium, potassium, magnesium, and other ions is essential to allow for the body to respond appropriately and in a timely fashion.

Vasopressors & Inotropes

- Vasopressors are agents that cause constriction of blood vessels, leading to increased blood pressure.
- Some drugs are also inotropes which also increase contractility
- Some are chronotropes which increase heart rate
- The hemodynamic effect these drugs have occur secondary to the interaction with the receptors in the cardiovascular system.
- Generally administered with the assumption that short to medium term improvement in hemodynamics will have a favorable long term outcome for the patient. Often times they are administered while other therapies or tests are performed to reverse or stop the cause of unstable hemodynamics.
 - Central line preferred, but may be given peripherally. Use largest gauge IV available preferably with blood return. Monitor site more frequently. If infusion continues longer than 24 hour, consider central line.

Hemodynamic Refresher



The Drugs



Clin Ops 13.420

- Guidelines for Administration of IV medications by Nursing
- A Baystate Medical Policy that is meant to guide the bedside nurse when administering intravenous medications that require a higher level and/ or frequency of monitoring.
- Maintained and reviewed by the Pharmacy and Therapeutics committee as well as representative of the medical and nursing teams.
- The titration guidelines in *the appendix* provide recommendations regarding the amount and frequency of titrations appropriate for each drug
- Review of **Key** and **Level of care** as well as how to read guidelines
- Specific drug information linked out to UptoDate and compatibility linked out to Micromedex. Lexicomp

Epinephrine

- Generic Name: Adrenalin
- Classification: Beta Adrenergic Agonist/ Potent inotrope and vasoconstrictor
- Use: Anaphylaxis, Cardiac Arrest, Low cardiac output
- IV Push in cardiac arrest only (1:10,000)
- Continuous infusion via infusion pump in critical care for Low Cardiac Output
- Subcutaneous or IM for anaphylaxis (1:1000 concentration only) at dose of 0.3mg
 - May be administered in all areas
- Potent vasoconstrictor and stimulant
- What to monitor: heart rate, BP (frequently), watch for chest pain or tightness, EKG changes such as ST elevation or increased ectopy, and dyspnea. May increase glucose levels.

Levophed

- Generic Name: Norepinephrine
- Classification: Adrenergic agonist/ Potent vasoconstrictor
- Use: Acute hypotension, septic shock
- IV Push: NO
- Continuous infusion via infusion pump in critical care
- Concentration 4mg/ 250ml D5W or NS
- Always ensure adequate volume status prior to initiating
- Central line administration strongly recommended
- Typical Starting Dose: 0.05-0.1 mcg/kg/min
- May go up to doses over 1.6mcg/kg/min in severe septic shock
- What to monitor: heart rate, BP (frequently), EKG changes such as ST elevation or increased ectopy, RR, and peripheral circulation.
- Infiltrates can cause tissue necrosis, extravasation and gangrene. Regitine may be injected into infiltrated tissue to reverse or stop damage to tissue with physician order.

Vasopressin

- Brand Name: Pitressin
- Classification: Vasoconstrictor
- Use: Acute hypotension, septic shock
- Continuous infusion via infusion pump in critical care
- Concentration: 40u/ 250ml 0.9 % NACL
- **Esophageal varices:** Infusion of 0.2-0.4 units/min (max 0.8 unit/min) then titrate. When bleeding stops continue for 12 hrs then taper off within 24-48hrs.
- **Diabetes insipidus:** SC 5-10 units every 6-8 hrs, Infusion of 1-3 units/hr
- **Septic Shock:** Infusion of 0.03 units/min
- **Postcardiotomy Shock:** Infusion of 0.01- 0.04 units/min
- **Caution:** Doses greater than 0.04 units/min should be used with extreme caution. Such high doses are associated with evidence of gut hypoperfusion (Anesth Analg 2001;93:7)

Neo-Synephrine

- Generic Name: Phenylephrine
- Classification: Adrenergic alpha agonist/ vasoconstrictor
- Use: hypotension and shock
- IV Push: in critical care with physician present or cardiac surgery with appropriate order
- Continuous infusion via infusion pump in critical care and PCU
- Vasoconstrictor
- Concentration 10-30 mg in 250ml D5W or NS
- Central line administration strongly recommended
- Typical Dose: 0.5-5 mcg/kg/min
- What to monitor: heart rate, BP (frequently), EKG changes such as ST elevation or increased ectopy, RR, and peripheral circulation.
- Infiltrates can cause tissue necrosis and extravasation. NaCl containing Phentolamine may be injected into infiltrated tissue to reverse or stop necrosis with physician order.

Dopamine

- Brand Name: Inotropin
- Classification: Beta Adrenergic Agonist/ inotrope and vasoconstrictor
- Use: hypotension and shock
- IV Push: NO
- Continuous infusion via infusion pump in critical care and intermediate care. Set rate below 3 mcg/kg/min in telemetry areas.
- Concentration: 400mg in 250 of D5W or NS
- Central line administration strongly recommended due to risk of necrosis and extravasation due to infiltrate.
- Dosing: low 1-3 mcg/kg/min, mid 3-15 mcg/kg/min, high > 15 mcg/kg/min
- What to monitor: BP, EKG, HR, IV site, electrolytes. Potential to cause cardiac irritability. Watch for increased ectopy and dysrhythmias. If this occurs and notify MD.

Dobutamine

- Brand Name: Dobutrex
- Classification: Beta Adrenergic Agonist/ inotrope
- Use: Heart failure, shock, low cardiac output
- IV Push: NO
- Continuous infusion via infusion pump in critical care and intermediate care. Set rate in telemetry areas if DNR/ refractory CHF.
- Central line administration strongly recommended
- Typical Dose: 2.5-20 mcg/kg/min
- What to monitor: BP, EKG, HR, IV site, electrolytes. Potential to cause cardiac irritability. Watch for increased ectopy and dysrhythmias. If this occurs stop infusion and notify MD.
- Works by lowering afterload (SVR) and increasing force of contraction as well as stroke volume.

Primacor

- Generic Name: Milrinone
- Classification: Inotropic vasodilating phosphodiesterase inhibitor
- Use: Heart failure, cardiogenic shock, low cardiac output
- IV Push: Yes
- Continuous infusion via infusion pump in critical care and intermediate care. Set rate in telemetry areas stable
- Typical Dose: .375-.75 mcg/kg/min
- Concentration: 20 mg/ 100ml D5W or NS
- What to monitor: BP, EKG, HR, ectopy, arrhythmias
- Works by lowering afterload (SVR) and increasing force of contraction as well as stroke volume
- End stage heart failure patients may go home on this or come in occasionally for rescue dosing.

Nitroglycerin

- Brand Name: Tridil
- Classification: Nitrate
- Use: Angina, CHF, hypertension
- IV Push: NO
- Continuous infusion via infusion pump in critical care and intermediate care.
- Concentration: 50-100 mg/ 250ml D5W
- Typical Dose: Up to 200 mcg/min
- What to monitor: BP, patient may be orthostatic
- Must be mixed in glass container and infused through **nitro** tubing.

Nipride

- Generic Name: Nitroprusside
- Classification: Fast acting and potent nitrate and vasodilator
- Use: Hypertensive crisis, heart failure
- IV Push: NO
- Continuous infusion via infusion pump in critical care and intermediate care.
- Typical Dose: 0.3-8 mcg/kg/min
- What to monitor: BP, continuously or frequent. If infusing longer than 48 hours, monitor thiocyanate level.
- Patient will be orthostatic on infusion.
- Must protect from light.
- Once mixed, drug will be light amber color.

Clevidipine

- Brand Name: Cleviprex
- Classification: dihydropyridine calcium channel blocker
- Use: Reduction of blood pressure when oral therapy is not feasible or desirable
- Continuous infusion via infusion pump in critical care and intermediate care.
- Concentration: 0.5mg/ml. Available in 50ml, 100ml, and 250ml bottles
- Typical Dose: Initiate at 1-2mg/hour. Dose may be doubled at short (90 second) intervals initially. As BP approaches goal, increments and time should lengthen to every 5-10 min. 1-2mg/hour increase will generally produce an additional 2-4mmHg decrease in systolic pressure. Max dose typically 16mg/hr, some short term data available up to 32mg/hr. Due to lipid load restrictions, no more than 100ml or 21mg/hr in a 24 hour period.
- What to monitor: BP and HR
- Contraindications: known allergy, defective lipid metabolism, & severe aortic stenosis.
- Must be changed every 12 hours

Esmolol

- Brand Name: Brevibloc
- Classification: Beta Adrenergic Blocker
- Use: SVT, hypertension, atrial arrhythmia
- IV Push: yes
- Continuous infusion via infusion pump in critical care and intermediate care.
- Typical Dose: 50-200 mcg/kg/min
- What to monitor: BP, EKG, HR, IV site, electrolytes.
- Typically short term use. Convert to PO metoprolol when patient stabilized.

Lidocaine

- Brand Name: Xylocaine
- Classification: Type IB antiarrhythmic
- Use: V-Tach, V-Fib, persistent ventricular ectopy
- IV Push: Yes (loading dose 1-1.5 mg/kg)
- Continuous infusion via infusion in critical care and intermediate care
- Central line administration strongly recommended
- Typical Dose: 1-4 mg/min
- What to monitor: BP, EKG, HR, RR, LOC
- Watch for bradycardia, heart block, decreased level of consciousness, confusion. Changes in LOC or CNS may be signs of lido toxicity. Especially with infusions lasting longer than 12 hours

Amiodarone

- Brand Name: Cordarone
- Classification: Class III antiarrhythmic
- Use: Sustained V Tach, Afib, or Vfib
- IV Push: Yes, in cardiac arrest due to VT or VF per ACLS guidelines
- Bolus dose: Yes, 150mg/ 100ml over 20 minutes in D5W
- Continuous infusion via infusion pump in critical care, intermediate care, and floors with telemetry.
- 900mg/ 500ml D5W @ 34ml/hr (1mg/min) for 6 hours Loading Dose, then 17ml/ hr (0.5mg/min) maintenance infusion.
- *Must use inline filter*
- Central line administration strongly recommended due to high rate of phlebitis. Other options are small IV in large vein
- What to monitor: BP, HR, IV site, and EKG, particularly QT interval.
- Will potentiate Warfarin and digoxin effects

Diltiazem

- Brand Name: Cardizem
- Classification: Calcium Channel Blocker
- Use: SVT, Afib, Aflutter, hypertension, and coronary artery spasm
- IV Push: Yes
- Continuous infusion via infusion pump in critical care, intermediate care, and floors with telemetry.
- Typical Dose: 2.5-20
- What to monitor: BP, EKG, HR
- Bolus dose: 0.25mg/kg over 2 min
- Continuous infusion: 5-15mg/hr
- Concentration: 125mg/ 125ml of D5W
- Monitor for bradycardia or heart blocks as well as hypotension.
- Convert to oral dosing after 24 hours if stabilized

Adenosine

- Brand Name: Adenocard
- Classification: Antiarrhythmic
- Use: PSVT, cardiac perfusion testing, EP lab, Cath lab
- IV Push: Yes, RAPID! May be given in monitored areas with MD present
- Make sure you have someone available to monitor airway and have patient attached to defibrillator/ pacer
- Continuous infusion: NO
- What to monitor: BP, EKG
- 6mg IVP (no slower than 1-2 seconds)
- Repeat dose of 12mg Q1-2 min X 2 doses.
- Running IV line may make administration more efficient

Lorazepam

- Brand Name: Ativan
- Classification: Benzodiazepine
- Use: Seizure control, alcohol withdrawal, anxiety, conscious sedation, anesthesia, adjunct antiemetic
- IV Push: Yes
- Continuous infusion: Yes
- What to monitor: BP, RR, LOC, Mental status, infusion site, @ high doses (>18mg/hr) watch for metabolic acidosis and renal dysfunction
- Adverse effects: hypotension, respiratory depression, apnea, pain at injection site
- Propylene glycol diluent prohibits IVP rate > 1ml/minute or 0.5mg/kg over 2-5 minutes and continuous infusion rate > 18mg/hr.
- Considerations: Long half-life makes reaching a steady state with continuous infusion take several days. Suggest more loading doses and IVP boluses to reach steady state faster.



Anti-Hypertensives

- Goals of treatment are to reduce morbidity, prevent complications and reduce end organ failure
 - Patients <60 and > 18 with chronic kidney disease (CKD) or diabetes have goal BP of approximately 140/90
 - Patients >60 without diabetes or CKD have BP goal of <150/90
- 2014 Eighth Report of The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 8) recommends that first line treatment include four main classes of medications
 - Thiazide-like diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs)

Thiazide Diuretics

- Act by inhibiting the sodium-chloride transporter in the distal tubule and also causing a chronic reduction in peripheral vascular resistance secondary to a reported vasodilatory effect
- Increase potassium and bicarbonate excretion and decrease calcium excretion and uric acid retention
- Tend to work well in patients of African descent and elderly
- Full benefit of reduced BP may take several weeks
- Not effective when GFR is < 25 ml/minute
 - Hydrochlorothiazide
 - Chlorthalidone
 - Metolazone/ Zaroxolyn
 - Indapamide/ Lozol

Potassium Sparing Diuretics

- Should be considered when maintaining normal serum potassium is important. Suppresses aldosterone-sensitive sodium reabsorption. Useful in patients with edematous conditions refractory to other diuretics, including liver cirrhosis, congestive heart failure and nephrotic syndrome.
- Research indicates that these medications can improve survival of hemodynamically stable patients with LV systolic dysfunction and heart failure after an acute MI
- Often used with loop or thiazide diuretics to prevent hypokalemia
 - Spironolactone/ Aldactone
 - Eplerenone/ Inspira
 - Amiloride/ Midamor

Loop Diuretics

- Not recommended in the initial treatment of hypertension
- Drug of choice when GFR < 25ml/min and in patients with hypertensive crises as well as an option for patients resistant to thiazides
- Inhibits reabsorption of sodium and chloride in the loop of Henle
- Rapid onset, but short duration
 - Furosemide Lasix
 - Torsemide Demadex
 - Bumetanide/ Bumex
 - Ethacrynic Acid/ Edecrin
- At high doses these drugs are ototoxic, especially in the setting of renal failure or when combined with aminoglycosides
- IV push should be administered slowly

Peripheral Alpha-Adrenergic Blocking Agents

- Selectively block alpha receptors on blood vessels, thereby inducing arterial and venous relaxation and lowering blood pressure.
- Never first choice for treatment of hypertension
- Use is limited by adverse effects
- Some patients with BPH (benign prostatic hypertrophy) and hypertension may benefit from this category of drugs.
 - Prazosin
 - Terazosin
 - Doxazosin
- Typically administered before bedtime to avoid orthostatic hypotension

Centrally Acting Adrenergic Agonists

- Stimulate sympathetic receptors in the brain and elicit a reduction in the peripheral sympathetic activity
 - Methyldopa/ Aldomet
 - Clonidine/ Catapres

Beta-Adrenergic Blocking Agents

- Because of lack of evidence, Beta Blockers are no longer a first line agent to treat htn.
- Hypertensive patients with heart disease and MI (myocardial Infarction) can benefit from Beta Blockers in several ways
 - Lower the heart rate, decrease oxygen demand, lower sympathetic tone
- Use with caution in patient with asthma, low ejection fraction, and heart failure
- Use with caution in patients who smoke or have Raynaud's as it may worsen peripheral ischemia
 - Atenolol/ Tenormin
 - Metoprolol/ Lopressor, Toprol
 - Propranolol/ Inderal
 - Nebivolol/ Bystolic

Combined Alpha/ Beta-Adrenergic Blockers

- Some studies show that these drugs can lower mortality in hypertensive patients with and MI or aortic dissection
 - Labetalol/ Normodyne, Trandate
 - Carvedilol/ Coreg

Peripheral Vasodilators

- Dilate blood vessels and lower blood pressure.
 - Hydralazine/ Apresoline
 - May be given PO and IV
 - 10 – 100 mg tablets available
 - Minoxidil/ Loniten
 - Effects are not clinically consistent
 - Used in refractory hypertension
 - 5-10 mg tablets available
 - Not used by women due to increased hair growth

Calcium Channel Blockers

- The Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure recommends first line treatment with CCB
- Dihydropyridine Type
 - The dihydropyridine CCBs bind to the gated calcium channels in cardiac and vascular smooth muscle resulting in vasodilation
 - Nifedipine/ Adalat
 - Amlodipine/ Norvasc
- Non-Dihydropyridine Type
 - The non-dihydropyridine CCBs also bind to the gated calcium channels in the right atrium and have potent effects on systemic arteries
 - Diltiazem/ Cardiaem
 - Verapamil/ Calan

Angiotensin-Converting Enzyme Inhibitors

- The Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure recommends first line treatment for hypertension to include ACEIs.
- ACEIs reduce angiotensin II, decreasing aldosterone. They slow resistance to arteries and increase venous capacity. The result is an increase in cardiac output and lowering of blood pressure.
 - Captopril/ Capoten
 - Ramipril/ Altace
 - Enalapril/ Vasotec
 - Lisinopril/ Zestril
- Most common side effect is dry cough

Angiotensin II Receptor Antagonists

- The JNC recommends that first line treatment for hypertension include ARBs as well as first line treatment for patients with hypertension and CHF symptoms
- Relatively newer and more expensive than ACEIs. Designed for patients that cannot tolerate ACEIs and is less likely to cause dry cough.
 - Azilsarta Edarbi
 - Losartan/ Cozaar
 - Calsartan/ Diovan

Anticoagulation

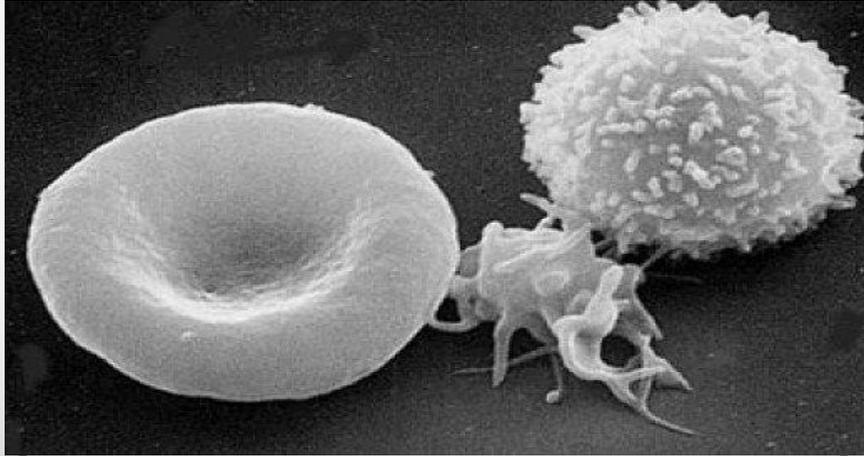
- Anticoagulation treatment is used to manage the majority of patients with DVT. The goal is to prevent the DVT from becoming a pulmonary embolism, thus decreasing morbidity and mortality.
- Patients with malignancies have a much higher rate of DVT than patients without cancer.

Types of anticoagulants

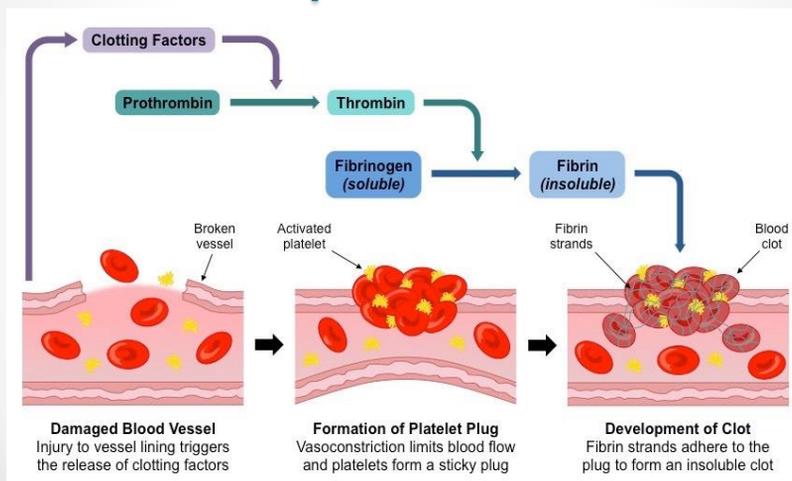
- Heparin- (reversal with protamine) interacts with anti thrombin III to inhibit thrombin formation
- Low Molecular Weight Heparin (LMWH)/ Lovenox- inhibits factor X
- Warfarin/ Coumadin- interferes with factor II, VII, IX, and X and the synthesis of vitamin K
- Thrombolytics- Used to dissolve clots by converting plasminogen to plasmin. Plasmin then breaks down the fibrinogen and fibrin contained within the clot.
- Streptokinase (non fibrin specific)
- Alteplase (TPA), Reteplase, and Tenecteplase (TNK)
- Always monitor for bleeding at site, hematuria, etc.

From left to right

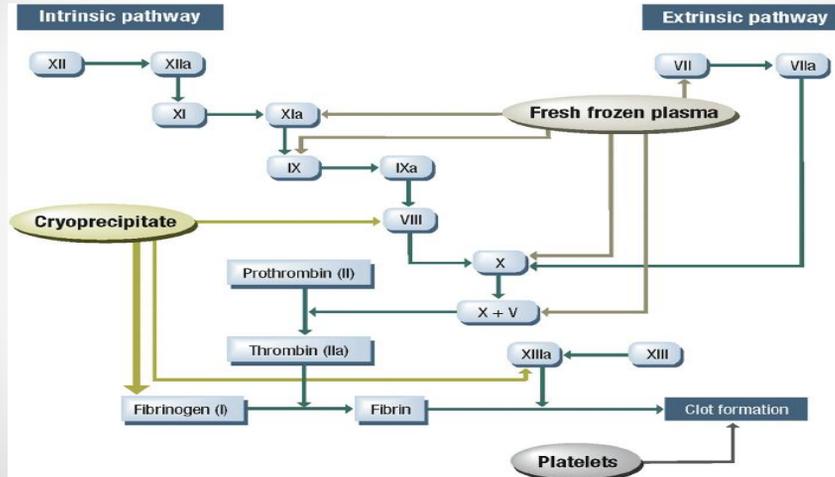
red blood cell, platelet, white blood cell



The development of a clot...



The clotting cascade and blood products



DVT and PE

- Each year, 600,000 patients will experience venous thromboembolism.
- Each year, at least 50,000 and perhaps as many as 200,000 patients will die from blood clots that obstruct blood flow to their lungs (pulmonary embolism).
- The tragedy is that most of these problems could be avoided by simple, cost-effective measures.
- Use of modern methods of DVT prophylaxis will reduce the incidence of DVT during the postoperative period by two-thirds and will prevent death from pulmonary embolism in 1 patient out of every 200 major operations.
- Using prophylaxis for DVT is neither complicated nor expensive.
- Giving prophylaxis to those who are at risk should be a routine practice in your hospital.
- the approach to DVT prevention is similar to preventing postoperative wound infections. You wouldn't allow a patient to miss a dose of antibiotic and you shouldn't allow them to miss a SQ heparin or lovenox dose either.

QUESTIONS? DISCUSSION...



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