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2. How do they work?

1. Inotropic Drugs

Inotropic drugs work by increasing the force of ventricular contraction, for indication impaired myocardial systolic function. Although each drug in this group work through a different mechanism they generally all work through to improve cardiac contraction by increasing intracellular calcium concentration. When the intracellular calcium is increased the cardiac actin / myosin interactions are augmented resulting in increased stroke volume and cardiac output for each ventricular filling.

a. Digitalis Glycosides (Digoxin)

- Digoxin is perhaps one the most commonly used cardiac glycoside, and has been studied extensively. Digoxin works by inhibiting the sarcolemma Na-K ATPase activity which results in an increase in the intra-cellular Na concentration. This results in an increase in trans-sarcolemma sodium gradient and increases the Na/Ca exchange. The end result is that the intracellular Ca concentration is increased, which means that more Ca is available to the contractile proteins. The myocardial response results in increased contractility and increased cardiac output. Similarly the increased intra-cellular sodium concentration delays repolarization and therefore decreases both sinus rate and AV conduction.

b. Sympathomimetic Amines

- Adrenergic agonists mimic the effect of the sympathetic nervous system. Stimulation of the Beta1-adrenergic receptors in the heart results in positive inotropic (increases contractility), chronotropic (increases heart rate), dromotropic (increases rate of conduction through AV node) and lusitropic (increases relaxation of myocardium during diastole) effects. The effects of the beta1 agonists are mediated by G-coupled protein stimulation which stimulates adenylyl cyclase and generates cAMP. The G-coupled protein stimulation ultimately results in the activation of cAMP-dependent protein kinases and the phosphorylation of key regulatory proteins in the cardiac myocytes.
- Care must be taken when prescribing these drugs in a pediatric setting. Several factors must be taken into consideration including: Loading conditions, volume status and responsiveness of peripheral vasculature. This can be especially tricky in critically ill infants and children. Furthermore, the exact titration of these drugs is further complicated by the fact that there are age dependent changes in receptor-effector coupling, kinase activities, substrate availability, phosphatase activity and cAMP hydrolysis by phosphodiesterases. These factors contribute to age related variability in responsiveness to the adrenergic agonists.

Examples of Sympathomimetic Amines:

Drug Name	Notes
Dopamine	Dopamine is an endogenous catecholamine precursor of epinephrine which is capable of directly and indirectly increasing blood pressure. Dopamine is administered as a continuous infusion. Dopamine has specific dopaminergic (DA) receptor effects at low concentrations, Beta1 receptor effects (positive inotropy and chronotropy) at moderate concentrations, and Alpha1 receptor effects (vasoconstriction) at high concentrations. Dopamine also causes renal vasodilation (controvercial).
Dobutamine	Dobutamine affects mainly the beta 1 adrenergic receptors. In children, Dobutamine increases the contractility and heart rate, thereby improving cardiac output. As a result, systemic vascular resistance may decline (secondary vasodilation). Dobutamine does not dilate renal vasculature. Dobutamine is often used in conjunction with Dopamine, considering the balancing effects on peripheral vascular resistance.

Isoproterenol	Isoproterenol is a synthetic catecholamine that is selective in Beta receptor agonism. Administration will result in the stimulation of both the Beta1 receptors found primarily in the myocardium as well as the peripheral Beta2 receptors. Administration of Isoproterenol increases cardiac contractility and heart rate via the Beta1 receptor stimulation, while reducing systemic vascular resistance as a result from the Beta2 stimulation. Isoproterenol reduces pulmonary vascular resistance and can help patients with pulmonary hypertension. Adverse side-effects include sinus tachycardia and arrhythmias and because of this patients must be monitored closely.

c. Phosphodiesterase Inhibitors

– Are drugs that control the degradation of intracellular cAMP. With increased intracellular cAMP levels the sarcoplasmic calcium concentration increases, resulting in increased cardiac muscle contractility (positive inotropy), with little effect on chronotropy. In the vasculature increased cAMP levels associate with smooth muscle relaxation and vasodilation.

Examples of Phosphodiesterase Inhibitors

Drug Name	Notes
Milrinone	Milrinone is a potent and selective Phosphodiesterase Inhibitor. Generally Milrinone tends to be better tolerated in the pediatric population than Amrinone, but may cause significant hypotension due to the vasodilating effect on peripheral vasculature. It can also cause thrombocytopenia with prolonged use. Dobutamine is often preferred to Milrinone in neonates, due to its better side effect profile.
Amrinone	A relatively weak and non-selective phosphodiesterase inhibitor. Long term oral therapy is associated with significant toxic effects. Not used often in pediatrics.

A comparison of the different types of Inotropic drugs

Class	Type	Examples	Predominant Agonist Effect	Contractility	After load	Heart Rate
Inotropic	Digitalis Glycosides	Digoxin	n/a Increases intracellular Ca.	↑↑		↓
	Sympathomimetic Amines	Dopamine,	Beta1=DA1>Alpha	↑↑	↑↑	↑↑
		Dobutamine,	Beta1	↑↑	(↓)	↑
		Isoproterenol,	Beta1=Beta2	↑	↓↓	↑↑↑
		Epinephrine,	Beta1=Beta2=Alpha	↑↑	↑↑	↑↑
		Norepinephrine	Beta1=Alpha		↑↑	
	Phosphodiesterase Inhibitors	Amrinone, Milrinone	n/a Increases cAMP, ↑intracellular Ca and vasodilate	↑	↓↓	(↑)

2. Vasodilator Drugs
   - Initial vasoconstriction is a mechanism used by the body to compensate for falling cardiac output. This vasoconstriction is mainly mediated by norepinephrine and angiotensin II. Venous constriction may ultimately result in pulmonary congestion as the pulmonary capillary hydrostatic pressure rises. Venous constriction can also result in an increase in the resistance against which the left ventricle must contract and thereby impedes cardiac output. Thus, vasodilator drugs are given to mediate the increased constriction and reduced the unwanted side effects of the compensatory mechanisms at work. These drugs can act to reduce elevated blood pressure and are therefore anti-hypertensives. Each of the vasodilator drugs work at specific vascular sites, and some (ACE inhibitors, alpha-blockers and sodium nitroprusside) are able to work on both sides of the circulation.

3. Anti-adrenergic Drugs
   - Normally stimulation of a sympathetic nerve results in norepinephrine being released and stimulating alpha or beta receptors.
   - Generally - each drug works by interfering with the sympathetic nervous system

4. Anti-arrhythmic Drugs
   a) Although a number of different classification systems exist, these drugs are commonly separated into four groups (Classes I through IV) based on their mechanism of action, and then there are those that do not fall into this classification scheme and are simply named (such as Adenosine)
      - The main reason to use these drugs is to abolish the mechanisms by which tachy-arrhythmias occur.
   b) Class I Anti-arrhythmics
      - Block the fast sodium channel responsible for phase 0 depolarization of the action potential
      - Further divided into three subtypes based on the degree of sodium channel blockade and the effect of the drug on the cell's refractory period
   c) Class II Anti-arrhythmics
      - Beta-adrenergic receptor blockers
   d) Class III Anti-arrhythmics
      - These drugs significantly prolong the action potential with little effect on the rise of phase 0 depolarization
      - The mechanism of action is through blocking the repolarizing potassium current during the phase 2 and phase 3 of the action potential
   e) Class IV Anti-arrhythmics
      - Block the slow L-type calcium channel
   f) Adenosine
      - An endogenous nucleoside with a very short half life
      - Most effective drug for the elimination of re-entrant PSVT
      - Binds to specific adenosine receptors and activates potassium channels. When the potassium channels are activated the inward potassium current hyperpolarizes the cell membrane and thereby suppresses spontaneous depolarization of the SA node as well as slows conduction through the AV node.

5. Diuretics

– Most often used to treat heart failure and hypertension and are considered to be the mainstay of anti-congestive therapy. With heart failure there is an enhanced renal re-absorption of sodium and water which results in peripheral edema and pulmonary congestion. Diuretics are used to relieve the congestive symptoms associated with the excess fluid in the extra-cellular space. The clinical response to a diuretic depends on how efficiently salt and water is delivered to the renal tubule.

a) Loop Diuretics
   - This type of diuretic works at the loop of Henle. At the loop of Henle the loop diuretics inhibit chloride-sodium-potassium co-transport in the thick ascending limb. This results in a reduction of the reabsorbed chloride, sodium and potassium, as well as a net increase in the excretion of free water.

b) Thiazide Diuretics
   - These work by inhibiting the sodium and chloride transport in the distal convoluted tubule of the nephron.

c) Potassium Sparing Diuretics
   - The potassium sparing diuretics are anti-congestive, i.e they increase the loss of water without sacrificing potassium.

d) Osmotic Diuretics
   - The osmotic diuretics are reserved for the acute setting. These are generally used in patients with severe circulatory congestion with limited renal output.

6. Anti-thrombotic Drugs

– Modulation of the platelet function and the coagulation pathway helps to control the pathogenesis associated with such cardiovascular disorders as unstable angina and acute myocardial infarction as well as such disorders as venous thrombosis, thrombi associated with atrial fibrillation, dilated cardiomyopathy or mechanical prosthetic heart valves

7. Lipid regulating Drugs

– Help to modulate the pathogenesis of atherosclerosis
– Drugs that improve lipid outcomes are cardioprotective and inhibit the progression of atherosclerosis

3. Considerations for the pediatric patient

– Oral administration of drugs is the most common method used in children. Neonates, compared with infants and older children have less acid secretion in the stomach for the first few weeks after birth. GI transit time is more rapid for the first 5 years of childhood and this can affect the absorption of drugs administered in a sustained release preparation

Drug distribution

– Drugs are distributed from the plasma to different organs on the basis of their affinity for tissues with high water or lipid content. For example in premature infants water represents 85% of BW whereas in the 1 year old child it represents 60%. When the percentage of extra-cellular water is high, as it would be in a neonate patient, a drug must be given in a larger dose n a milligram per kilogram basis to achieve the same serum concentration

The amount of body water changes with development

Age	Extra-cellular Water (%)	Total Body Water (%)
Premature Infant	60	85
Full term infant	55	75
5-month old child	50	60
1 year old child	40	60
Adolescent	40	60

Drug Metabolism

– Predominantly done in the liver
– 2 major pathways:
  - Phase 1: metabolize substances and consist of the mixed function oxidase system, the cyp450 system and the N-demethylation pathways.
    - Premature and full term neonates have 50 to 75% of these enzymes compared to levels in infants.
    - This means that drugs metabolized by these systems may have a higher serum concentration for the same relative dose in neonates as compared to infants
  - Phase 2: reactions conjugate endogenous compounds or specific drugs and their metabolites into water soluble entities by glucuronidation, or acetylation.
    - These are usually adequate to metabolize most drugs and endogenous compounds by 1 to 2 weeks after birth in full term infants
    - Doses of certain drugs must be adjusted accordingly in the first few weeks of neonatal life or else the neonate may be predisposed to drug toxicity

Drug elimination

– The primary route of drug elimination of drugs is via the kidney. Drug elimination can also occur via the biliary, GI and respiratory tracts to a lesser degree. There is decreased renal elimination in neonates which must be accounted for when dosing Rx.

Development of the kidney in children

Age	GFR (mL/Min/1.73M2)	Max tubular secretion (mg/min/1.73)
Full term neonate	33	16
1 month	50	30
2 month	70	50
6 month	110	60
3 years	130	75

Usual therapeutic and toxic serum drug concentrations

Cardiovascular agent	Therapeutic level	Toxic level
Digoxin	0.5 to 2 ng/mL	>3 ng/mL
Lidocaine	2 to 5 μg/mL	>6 μg/mL
Quinidine	1 το 5 μg/mL	>7 μg/mL
Procainamide	4 το 10 μg/mL	>10 μg/mL

4. Summary Table

Class	How do they work?	Type	Examples
Inotropic	– Increase the force of the ventricular contraction when myocardial systolic function is impaired – Generally all drugs in this class improve cardiac contraction by increasing intracellular calcium concentration via various mechanisms – Increased calcium serves to augment actin and myosin interactions in the cardiac muscle and thereby serves to increase the stroke volume and cardiac output for each ventricular filling.	Digitalis Glycosides	Digoxin
		Sympathomimetic Amines	Dopamine, Dobutamine, Isoproterenol, Epinephrine, Norepinephrine
		Phosphodiesterase Inhibitors	Amrinone, Milrinone
Vasodilator	– Mediate the increased constriction and reduced the unwanted effects of the compensatory mechanisms at work in the heart. – Act to reduce blood pressure and are therefore anti-hypertensives – Each of the vasodilator drugs work at specific vascular sites, and some are able to work on both sides of the circulation.	– Angiotensin-Converting Enzyme Inhibitors – Angiotensin II type 1 Receptor Antagonists – Direct-acting vasodilators – Calcium Channel Blockers – Organic Nitrates	- Enalapril, Captopril - Losartan - Digoxin - Verapamil - Nitroprusside
Anti-Adrenergic	– Normally stimulation of a sympathetic nerve results in norepinephrine being released and stimulating alpha or beta receptors. – Generally - each drug works by interfering with the sympathetic nervous system	– Central adrenergic inhibitors – Sympathetic Nerve Ending Antagonists – Peripheral Alpha-adrenergic receptor antagonists – Beta-adrenergic receptor antagonists	Salbutamol (Beta 2 blocker) Prazosin (Alpha 1 blocker)

<table>
<tr><td rowspan="4">Anti-Arrhythmic</td><td rowspan="4">– Although a number of different classification systems exist, these drugs are commonly separated into four groups (Classes I through IV) based on their mechanism of action.
– The main reason to use these drugs is to abolish the mechanisms by which tacharrhythmias occur.</td><td>Class I Anti-arrhythmics
– Block the fast sodium channel responsible for phase 0 depolarization of the action potential
– Further divided into three subtypes based on the degree of sodium channel blockade and the effect of the drug on the cell's refractory period
o Class IA (medium blockade)
o Class IB (minimal blockade)
o Class IC (maximal blockade)</td><td>1A – Procainamide
1B – Lidocaine
1C - Propafenone</td></tr>
<tr><td>Class II Anti-arrhythmics
– Beta-adrenergic receptor blockers</td><td>Propranolol</td></tr>
<tr><td>Class III Anti-arrhythmics
– These drugs significantly prolong the action potential with little effect on the rise of phase 0 depolarization
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		Adenosine – An endogenous nucleoside with a very short half life – Most effective drug for the elimination of re-entrant PSVT – Binds to specific adenosine receptors and activates potassium channels. When the potassium channels are activated the inward potassium current hyperpolarizes the cell membrane and thereby suppresses spontaneous depolarization of the SA node as well as slows conduction through the AV node.	Adenosine
Diuretics	– Most often used to treat heart failure and hypertension and are used to relive the congestive symptoms associated with the excess fluid in the extra-cellular space	– Loop Diuretics – Thiazide Diuretics – Potassium-sparing Diuretics	– Furosemide – Hydrochlorothiazide – Spironolactone
Anti-thrombotic Drugs	– Modulation of the platelet function and the coagulation pathway helps to control the pathogenesis associated with such cardiovascular disorders as unstable angina and acute myocardial infarction as well as such disorders as venous thrombosis, thrombi associated with atrial fibrillation, dilated cardiomyopathy or mechanical prosthetic heart valves	– Platelet inhibitors – Anti-coagulant Drugs	– Tissue Plasminogen Activator – Warfarin, Heparin
Lipid regulating Drugs	– improve lipid outcomes are cardio-protective and inhibit the progression of atherosclerosis	– HMG CoA Reductase Inhibitors – Bile Acid Binding Agents – Niacin – Fibrates	

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