

Knowledge objectives for Cardiovascular Pharmacology

CALCIUM ANTAGONISTS.

Intracellular calcium concentration is tightly control by a number of mechanisms, including Ca^{2+} ATPase, Na^+ -driven Ca^{2+} antiport, compartmentalization of calcium into mitochondria, and Ca^{2+} sequestering compartment, and inactivation of free calcium by Ca^{2+} binding proteins.

Ca^{2+} entry into the cell occurs via receptor-dependent entry via voltage-dependent Ca^{2+} channels. There are three major types of voltage-dependent Ca^{2+} channels: L-type, long lasting, T-type, transient, and N-P-type.

Alpha subunit of L-type Calcium channel is a major target of Calcium Antagonists.

Molecular biological studies of alpha subunit of L-type Ca channels determined domains responsible for channel inactivation, excitation/contraction coupling, voltage sensing, and binding sites of three major group of Ca antagonists:

NIFEDIPINE, VERAPAMIL, AND DILTIAZEM.

Ca antagonists reduce probability of Ca^{2+} channel opening.

Ca antagonists selectively interact with L-type channels in vessels and heart.

As a result of vascular selectivity, Ca antagonists increase coronary perfusion that leads to improved oxygen supply. They also decrease peripheral vessel resistance that leads to decrease in blood pressure. Together, these effects result in improved heart performance.

Because of their properties, Ca antagonists are used in treatment of angina and hypertension. Verapamil and diltiazem that have selectivity to sino-atrial node can be used in treatment of supraventricular dysrhythmia.

New calcium antagonists have selectivity toward T-type calcium channels. They do not have negative inotropism; they do not have sympathetic activation. They can reduce heart rate, they are highly selective towards coronary vessels, they have minimal side effects.

DRUG TREATMENT OF HEART FAILURE

Positive Inotropic agents

- used in conjunction with diuretic agents, ACE inhibitors, vasodilators
- increase cardiac output (at constant preload and heart rate)
- increase intrinsic contractility of heart

Cardiac glycosides

- increase cardiac contractility by direct action on cardiomyocyte
- (Na,K)-ionic pump is receptor for cardiac glycoside
- *digoxin* and *digitoxin* are commonly used glycosides
- antiarrhythmic action against supraventricular arrhythmia: slowing of A-V conduction (negative dromotropic effect)
- negative chronotropic action: due to reflex bradycardia (vagal effect)
- *indications*: for use in low output heart failure particularly when atrial arrhythmias are present
- digitalis toxicity: ventricular tachyarrhythmias; gastrointestinal upset; CNS symptoms such as dizziness, convulsion

ANTIARRHYTHMIC AGENTS

Know the four classes of antiarrhythmic drugs. Note that side effects of overdoses of these drugs is often arrhythmia.

1. Group I: Na channel blockers. Useful for treatment of ventricular tachyarrhythmia and occasionally atrial tachyarrhythmia
2. Group II: Beta-adrenoceptor blockers. Useful against supraventricular tachyarrhythmias.
3. Group III: Action potential prolonging agents. Used against ventricular arrhythmias due to reentry circuits. *Bretyllium* is a 'chemical defibrillator'.
4. Group IV: Calcium channel blockers. Highly effective in treatment of supraventricular tachyarrhythmias.

ANTIANGINA AGENTS

These substances are for symptomatic treatment of angina.

Know the three basic mechanisms of anti-anginal drugs:

1. *Nitrates and nitrites*.: Nitroglycerin and related substances restore oxygen supply-demand balance through redistribution of coronary flow, reductions in preload, afterload, and total peripheral resistance.
- *Beta-adrenoceptor blockers* reduce cardiac contractility and heart rate by antagonizing beta-effects of endogenous catecholamines, thus resulting in diminished myocardial oxygen consumption.
- *Calcium channel blockers* reduce afterload and thereby decrease oxygen demand of the heart.

ANTIHYPERTENSIVE DRUGS

Know classification of antihypertensive drugs (AHDs) based on their mechanisms.

Think about how blood pressure (BP) is maintained:

$BP = \text{cardiac output (CO)} \times \text{peripheral vascular resistance (PVR)}$. Therefore, the anatomical sites of action for these drugs are heart, kidney, blood vessels, and part of the brain.

Why diuretics have been used as first-line AHDs? How are they further divided into 3 groups based on mechanisms of action? Know why they are useful when combined with several other AHDs.

α -agonists and blockers:

Know the difference between α_1 and α_2 adrenergic receptors. What are the sites of actions? Know how centrally acting AHDs work and what are the common adverse effects.

Know the basic mechanism of peripherally-acting AHDs is to block one or more key steps of sympathetic neurotransmission. Examples:

- β -blockers: To antagonize β_1 and/or β_2 -AR, therefore reduce CO and PVR.
- α_1 -blockers: To antagonize α -AR and reduce PVR.
- Ganglion-blockers: To block both sympathetic and parasympathetic ganglia, and nicotinic cholinergic receptors on postganglionic neurons.
- Blocking adrenergic neurotransmitter synthesis (reserpine) and release (guanethidine): The net effect is depletion of NE and reduced PVR and CO.

For direct vasodilators, know their clinical usage and their action mechanisms. Why these are not commonly used as first-line drugs?

Know how ACE inhibitors and angiotensin-II receptor antagonists work. What is the major difference between these two drugs in their action? What are the major adverse effects?

Know why more than one drug is often given to patients with moderate or high level of hypertension. Give several examples for the benefit of combined use of AHDs.

What kind of medications should be avoided if a patient is to take AHDs (sort out by different categories of AHDs)?

CHEMOTHERAPY

Selective Toxicity and Resistance - General Principles

Refer to your handout and know:

Definitions (Chemotherapy, Selective Toxicity, Chemotherapeutic Index)

General bases for selective toxicity

The table in the handout summarizes the important ones for the drugs we are presenting

General bases for drug resistance (again summarized in h.o.)

How R-factor plasmids work

How environmental antibiotics encourage the development of multiresistant microorganisms

Sulfonamides:

Know the basic sulfonamide structure and how it relates to PABA

Know in a general way the folate synthesis pathway, and where it is affected by sulfonamides and trimethoprim

Know why they are selectively toxic to microorganisms

Important factors of disposition are: rapid absorption, high degree of plasma protein binding, metabolism, elimination.

Know major toxicities and side effects (ESP. Hematological and dermatological)

How do bacteria become resistant?

Compare mechanism of action of trimethoprim to that of SA's

What combinations are used

Why is this an effective combination

Know short acting vs. long acting

Know names of 4 major short acting and 1 long acting

Why are non-absorbable SA's used?

Major uses for bacterial and non-bacterial infections

Quinolones (oxacin drugs)

What is their common structural feature?

How do they work?

Why are they selectively toxic?

What side effects are known?

What is their general clinical usefulness?

Antifungal Drugs

Know the mechanisms of action, side effects, and major modes of administration (topical and/or systemic) for the following types of antifungal drugs:

- 1) Polyene antibiotics
- 2) Azoles
- 3) Flucytosine
- 4) Griseofulvin
- 5) Echinocandins

Know the main principles of treatment for oral candidiasis infections

ANTIBACTERIAL ANTIBIOTICS

1. Know the components of bacterial cell wall, basic processes of cell wall synthesis and maintenance, and basic processes of bacterial protein synthesis.

2. Know the mechanism of antimicrobial activity for penicillins, cephalosporins, bacitracin, cyclosporin, aztreonam, imipenem, aminoglycosides, tetracyclines, chloramphenicol and the macrolides.
3. Know the classification of penicillins and cephalosporins according to their chemical structure and their antimicrobial spectrum. Know lactamase resistant forms.
4. Know the most common adverse effects of the antimicrobial drugs.
5. Know the mechanisms of bacterial resistance for antimicrobial drugs.
6. Know the most common applications of these antibiotics for the treatment of disease.

ANTINEOPLASTIC, ANTIVIRAL AND IMMUNOSUPPRESSANT DRUGS

Antineoplastic drugs

1. If given the name of an antineoplastic, know how to place it in a specific class. Know the mechanism of cytotoxicity of the different classes.
2. Most antineoplastics inhibit bone marrow function. Remember the exceptions to this rule, e.g., vincristine, asparaginase, bleomycin.
3. Know how resistance can develop and specific drug interactions.

Immunosuppressant drugs

1. Know different classes of immunosuppressants.
2. Know which drugs interfere with T or B cell function as well as their uses and toxicities.
3. Know the most common side effects.

Antiviral drugs

1. Know which antiviral agents are used to treat influenza, herpes or HIV. Within each class, the drugs are listed in order of their relative importance.
2. Know which antiviral agents are not analogs of nucleosides.
3. Know the rationale for using nucleoside analogs and their mechanisms as antiviral agents.
4. Know the most common side effects.