DRUGS THAT AFFECT CARDIOVASCULAR SYSTEM

University Of Nairobi

Department Of Public Health, Pharmacology & Toxicology

JPT 341 Pharmacology &Toxicology

BVM 3RD Year Lecture Notes

Dr Aboge, G.O. BVM, Msc, PhD

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Lecture objectives

1. By the end of this lecture the students should be able;

   - ❖ To list or give examples of the drugs that act on the cardiovascular system.

   - ❖ To describe the mechanisms of action of the drugs and their resulting pharmacological effects

   - ❖ To explain how the drugs are relevant in clinical medicine

Lecture outline

- Introduction
- Digitalis and related cardiac glycosides
- Parasympathomimetic drugs
- Sympathomimetic drugs
- Adrenoceptor blocking drugs (antagonists)

Lecture outline

- Anticholinergic or Belladona alkaloids
- Xanthines
- CNS stimulants
- Histamines
- Other drugs affecting cardiovascular functions

Introduction

- Cardiovascular systems consists of the heart, blood vessels and circulating blood.

- The system (heart) pumps blood to body tissues and distributes nutrients and oxygen.

- Drugs that act on the system are used to correct congestive heart failure, pulmonary oedema, hypertension and hypotension.

Digitalis and related cardiac glycosides

- They include;

  a). Digitoxin produced by *Digitalis (D) purpurea* and *D. lanta* (leaf).

  b). Digoxin from the leaf of *D. lanta*.

  c).Ouabain, (from the seed of *Strophanthin gratus)*.

Mechanism of actions of cardiac glycosides

- They inhibit Mg^{2+}-dependent Na^+/K^+-ATPase involved in exchange of Na^+ / K^+ ions in the heart leading to a reduced exchange of Na^+ / K^+ ions in myocardial cells.

- Ultimately, intracellular Na^+ ions increases with concomitant increase in concentration of Ca^{2+} ions.

- The elevated intracellular ca2+ ions concentration reduces resting membrane potential to less negative value.

Pharmacological effects of cardiac glycosides

- The drugs increase the force of the myocardial contraction (or positive inotropic effect).

- In a failing heart, digitalis glycosides increase systolic emptying.

- They also diminish residual ventricular volume, elevate cardiac output and reduce the size of the heart.

Pharmacological effects of cardiac glycosides

- They increase myocardial contractility and stroke volume with reflexogenic withdrawal of vasomotor tone.

- Consequently, peripheral vasodilation occurs leading to improved peripheral perfusion and tissue oxygenation.

Parasympathomimetic (cholinergic) drugs

- These drugs include;
  - ❖ Physiological acetylcholine,
  - ❖ Methacholine,
  - ❖ Bethanechol
  - ❖ Carbechol.

Mechanism of action and pharmacological effects on CVS

- **Parasympathomimetic** drugs stimulate muscarinic receptors (cholinergic receptors) in the heart and reduce heart rate and contraction force.

- On I.V administration, methacholine activates muscarinic receptors of blood vessels and heart.

- This stimulation also reduces atrial conductivity and conduction velocity of atriovetricular node (AVN).

Mechanism of action and pharmacological effects on CVS

- In small doses acetylcholine causes direct activation of muscarinic receptors of vascular smooth muscle

- Parasympathomimetic drugs cause brief and rapid fall in diastolic and systolic blood pressures due to reduced peripheral blood flow resistance.

- Methacholine has a more cardiovascular activity reducing conduction of impulses from the pacemaker and is good for treatment or controlling tachycardia of atrial origin

Sympathomimetic (adrenergic) drugs

- The drugs include;
  - ❖ Adrenaline & noradrenaline,
  - ❖ Isoprenaline, dopamine & dobutamine
  - ❖ Dopexamine, methoxamine & meteraminol.

Mechanism of actions of adrenergic drugs on CVS

- Adrenergic drugs stimulate α_1 α_2, β_1 and β_2 - adrenoceptors located in the heart and arteriole smooth muscles.

- Stimulation of cardiac β_1 adrenoceptors mediates the effects of stimulation of sympathetic nerves.

- Stimulation of cardiac β_2 adrenoceptors mediates the effects of circulating catecholamines.

General pharmacological effects of adrenergic drugs on CVS

- The stimulation of β-adrenoceptors in the heart cause increased rate, automaticity and increased velocity in conducting tissue. Myocardium contractility and oxygen consumption is also increased.

- α_1 adrenoceptors stimulation causes constriction of arterioles due to contractions of their vascular smooth muscles. β_2 adrenoceptors stimulation causes dilation of due to vascular smooth muscle relaxation

Pharmacological effects of specific adrenergic drugs

- Adrenaline stimulates both α and β – adrenoceptors causing constriction of arterioles (vasoconstriction).

- Noradrenaline stimulates α adrenoceptors causing contraction of arteriole smooth muscles and vasoconstrictions leading to increased blood pressure.

- Isoproterenol is a non-selective β-adrenoceptor agonist and strongly stimulate the heart. Dopamine activates α_1 & β_1-adrenoceptors causing noradrenaline release from nerve ending.

Pharmacological effects of specific adrenergic drugs

- Dobutamine is mainly β_1 adrenoceptor agonist with greater inotropic effect on the heart.

- Dopexamine is a cardiac β_{2-} adrenoceptor agonist with positive inotropic effect.

- Methoxamine and metaraminol directly act on peripheral α adrenoceptors and are potent pressure agents resistant to COMT and MOA metabolism, hence they have long acting effect.

- Methoxamine has been used as antihypertensive agent especially in anaesthetized animals.

Adrenoceptor blocking drugs (antagonists)

- These drugs are classed as;

a) *α and β adrenoceptors antagonists* including . propranolol, oxprenolol and labetalol

b). *α-adrenoceptors-specific antagonists* including prazosin, phentolamine, phenoxybenzamine and yohimbine.

c). *β-adrenoceptors-specific antagonists*, which include atenolol, metoprolol, betaxolol, practolol and pindolol

Mechanism of actions of adrenergic antagonists on CVS

- α-adrenoceptor antagonists block the α_1 and α_2 adrenoceptors on the effector organ. β – adrenoceptors antagonists selectively block β receptors effect of adrenaline.

- The drugs have cardiac effects resulting from reduction of sympathetic drive characterized by reduced heart rate and myocardial contractility.

- Propranolol, oxprenolol and labetalol have quinidine-like or local anaesthetic activity with membrane stabilizing activity.

Pharmacological actions of specific adrenergic blocking drugs on the CVS

- *Prazosin*, blocks postsynaptic α_{1-} adrenoceptors but not the presynaptic α_2 adrenoceptors.

- Therefore, α_2 adrenoceptor is spared so that negative feedback inhibition of noradrenaline release is maintained resulting in antihypertensive effect making the drug antihypertensive drug,

- *Phentolamine* is a non-selective α-adrenoceptor antagonist, and directly cause vasodilation and cardiac inotropic action. It is used for management of adrenergic hypertensive crises in man.

Pharmacological actions of specific adrenergic blocking drugs on the CVS

- *Phenoxybenzamine* is a powerful, long acting and non-selective α_2 adrenoceptor blocking drug.

- *Ergot alkaloids* and *chlorpromazine* are other α_2 adrenoceptor antagonists.

- *Atenolol*, *metoprolol*, *and betaxolol* have higher affinity for cardiac β_1-receptors than for β_2-receptors in cardic and peripheral blood vessels. Therefore, the drugs are cardioselective.

Pharmacological actions of specific adrenergic blocking drugs on the CVS

- *Practolol, and pindolol* are β antagonists with some partial agonist effect.

- They cause less fall in heart rate while resting or exercising than pure antagonists

Anticholinergic drugs that act on CVS

- These drugs include;
  - ❖ Atropine sulphate,
  - ❖Hyoscyamine,
  - ❖Hyoscine
  - ❖Homatropine.

Mechanism of action and pharmacological effects of anticholinergic drugs on CVS

- These drugs occupy muscarinic receptors in a prolonged manner and deny acetylcholine and other cholinergic drugs receptor sites in a competitive manner.

- This effect is reversed when concentration of acetylcholine and other cholinergic drugs is increased.

Mechanism of action and pharmacological effects of anticholinergic drugs on CVS

- Consequently, the drugs supress the vagal influence on the pacemarker resulting in tachycardia by exerting direct effect of sympathetic system.

- There is a slight increase in cardiac output due to transient vagal stimulation that may cause slight bradycardia.

Xanthines that act on CVS

- These drugs occur in plants and they include.
  - ❖ Caffeine,
  - ❖ Theophylline
  - ❖ Theobromine

Mechanism of actions and pharmacological effects on CVS

- ***Xanthines*** such as caffeine and theophylline directly stimulate the myocardium and cause increased cardiac output, tachycardia and, sometimes ectopic beats and palpations.

- The drugs cause peripheral vasodilation due to direct action of the drugs on the blood vessels. This vasodilation may be countered by stimulation of vasomotor centre resulting in unpredictable changes in blood pressure.

Mechanism of actions and pharmacological effects of central nervous system (CNS) stimulants on CVS

- *Amphetamine* act by releasing noradrenaline stored in nerve endings in both the CNS and the periphery.

- This brings about sympathetic effect on the heart causing palpitations, increasing peripheral oxygen consumption and vasodilation.

Mechanism of actions/pharmacological effects of histamine on CVS

- *Histamine:* **S**timulates H_1 and H_2 histamine receptors.
  - ❖ The pharmacological effects include dilation of terminal arterioles, capillaries and venules, increased capillary permeability leading to oedema.
  - ❖ Stimulation of the receptors cause contraction of large arteries and vein especially hepatic vein and pulmonary artery in the cat.

Mechanism of actions/pharmacological effects of histamine on CVS

- *Histamine* also causes short lived hypotension, reduced peripheral vascular resistance due to plasma loss and tachycardia.

- Histamine elicits positive inotropic and chronotropic effects due to realise of noradrenaline from nerve endings.

- They also direct activation of H2 receptors in the heart muscle in isolated heart muscle.

Other drugs affecting cardiovascular functions

- ***Class IA drugs***: They blocks sodium channel with prolonged refractoriness.

- These drugs restrict the rapid inflow of Na+ ions during phase zero and thus slow the maximum rate of depolarisation.

- They stabilize membrane activity and limit the responsiveness to excitation of cardial cells. Examples are *quinidine* and *procainamide.*

Other drugs affecting cardiovascular functions

- *Class IB drugs:* They block sodium channel and have shortened refractoriness.

- The drugs include lignocaine, mexiletine, tocainide and phenytoin.

- *Class IC drugs*: These drugs block sodium channels with minimal effect on refractoriness.

- Examples are flecainide and propafenone.

Other drugs affecting cardiovascular functions

- ***Class II drugs:*** These include catecholamine blockers and they reduce automatic discharge (phase 4).

- ***Class III drugs:*** Lengthens refractoriness without effect on sodium ion inflow in phase 0.

- They also prolong cellular refractoriness and examples are amiodarone and bretylium.

Other drugs affecting cardiovascular functions

- ***Class IV drugs***: These are ca2+ channel blockers.

- They supress slow inward ca2+ current and prolong conduction and refractoriness, especially in sino-arteriol and arteriovetricular nodes.

- An example is verapamil

Application of cardiovascular drugs in clinical medicine

- Digoxin and quinidine, can be used to control signs of congestive heart failure and cardiac arrhythmias in cattle.

References

- Veterinary Pharmacology and Therapeutics

- Applied Veterinary pharmacology and Therapeutics by *Jim E. Riviere and Mark G. Papich(Ed.)*. 9th Edition