UNIT 3 DRUGS ACTING OF AUTONOMIC NERVOUS SYSTEM

Structure

3.1 INTRODUCTION

The autonomic nervous system functions largely below the level of consciousness and controls visceral functions. They mediate visceral pain as well as cardiovascular, respiratory and other visceral reflexes. The motor limb of the ANS is anatomically divided into sympathetic and parasympathetic.

Objectives

After studying this unit, you should be able to:

- main drug acting on the cholinergic and sympathetic system, the prototype drug is described in detail and other drug of same group is described in short;
- differentiate between the actions of the cholinergic and sympathetic nervous system on different organs;
- enumerate the uses of different agonist and antagonists acting on the autonomic nervous system; and
- the side effects and overdose of these agents.

3.2 CHOLINERGIC AGENTS

These are the drugs which stimulate the parasympathetic system and mimic the action of acetylcholine. The acetylcholine receptor stimulants and cholinesterase inhibitors together comprise a large group of drugs that imitate the action of acetylcholine.

Bronchial asthma

It is a respiratory disease characterized by difficulty in breathing. It is due to constriction of bronchiales and increased in bronchial secretion.

3.2.1 Acetylcholine

Acetylcholine (Ach) is an ester of choline and acetic acid. It is extremely hygroscopic and rapidly undergoes hydrolysis in a neutral or alkaline medium. It is synthesized within the cholinergic neurons by the action of a specific enzyme 'choline acetylase'. Acetylcholine decreases the contractility (negative inotropy) and decreases the conduction velocity of the atria. It decreases the heart rate (negative chronotropy) and may cause cardiac arrest. Acetylcholine causes increase in tone, amplitude of contractions, peristalsis and secretory activity of the gastrointestinal tract. It also causes contraction of urinary bladder. Acetylcholine causes bronchoconstriction and increase in bronchial secretion and can precipitate bronchial asthma. Acetylcholine increases the salivary, sweat, lacrimal, nasopharyngeal, gastric and bronchial secretions. Because of nonselective and short duration of actions, acetylcholine is not used for any therapeutic purpose.

3.2.2 Other Cholinergic Drugs

Pilocarpine

It is a natural alkaloid obtained from leaves of *Pilocarpus microphyllus* and *Pilocarpus jaborandi.* Pilocarpine is direct acting muscarinic agonist. It produces contraction of iris to produce miosis. It also stimulates ciliary muscle resulting in increased accommodation and improved outflow of aqueous humor. Thus it is useful in treatment of glaucoma.

Ibopamine

It is a newer compound, producing dose-dependent mydriasis endowed with very interesting characteristics: rapid onset, marked pupil dilatation and rapid return to normal capillary diameter. It is approved for mydriasis in ocular examination and surgery and for the early diagnosis of glaucoma.

Arecoline

It is obtained from the betel nut and has got muscarinic and weak nicotinic actions. It has no therapeutic value except for chewing to promote salivary secretion and in pan masala etc.

3.2.3 Anticholinesterases

These are the drugs which act by inhibiting the enzymes, true and pseudocholinesterase and thereby produce an accumulation of acetylcholine at the various cholinergic sites. Anticholinesterase inhibits this enzyme which

results in accumulation of acetylcholine and continuous stimulation of muscarinic and nicotinic receptors.

The **reversible anticholinesterases** have a structural resemblance to acetylcholine, are capable of combining with cholinesterase as well as with acetylcholine receptor.

Irreversible cholinesterases are mostly organophosphorus compounds and combine only with cholinesterase and the enzyme gets phosphorylated. Because of the irreversible nature, their therapeutic usefulness is very limited. Most of the compounds are used as insecticides e.g. parathion, malathion.

Myasthenia gravis:

A chronic disease characterized by muscular weakness and rapid fatigability of the skeletal muscles due to impaired neuromuscular transmission.

Reversible Anticholinesterase

Physostigmine

It is a tertiary ammonium alkaloid obtained from the Calabar bean, which is indigenous to tropical West Africa. The actions of physostigmine are similar to those of cholinergic drugs. Topical instillation into the eye produces miosis and decrease in intraocular pressure. The main therapeutic use of physostigmine is as miotic to treat glaucoma and also to reverse the mydriatic effect of atropine and its analogues used in refraction of the eye.

Neostigmine

It is a synthetic quarternary ammonium compound, similar to physostigmine and rapid onset of action and can inhibit both true and pseudocholinesterases. On local ophthalmic administration, it produces miosis, spasm of accommodation and reduction in intraocular tension. Neostigmine is a drug of choice in the treatment of **myasthenia gravis**, a chronic disease characterized by muscular weakness and rapid fatigability of the skeletal muscles due to impaired neuromuscular transmission.

Pyridostigmine

It structurally and pharmacologically resembles neostigmine but has longer duration of action and less potent than neostigmine and better tolerated by myasthenia gravis patients.

Irreversible Anticholinesterases

The organophosphorus cholinesterase inhibitors like diisopropyl fluorophosphate, phospholine, parathion, malathion etc. are highly toxic compound and cause irreversible inhibition of both true and pseudo cholinesterase. They are highly lipid soluble compound and can easily cross the blood-brain barrier.

Diisopropyl Fluorophosphate (DFP)

The pharmacological effects are those of acetylcholine. It produces prolonged inhibition of true and pseudo cholinesterases. They are mainly **used** for the treatment of glaucoma, especially when other miotic agents fail.

3.3 ANTICHOLINERGIC AGENTS

Anticholinergic or cholinergic blocking agents are the agents which block the action of acetylcholine at the postganglionic parasympathetic nerve endings. The nicotinic antagonists also block certain actions of acetylcholine and are termed as ganglion blocking agents.

Cycloplegia

The condition in which, one can see things clearly only at a long distance and can not constrict the pupil for viewing the near objects clearly.

3.3.1 Atropine

The alkaloids namely atropine, hyoscyamine and scopolamine are obtained from *Atropa belladonna*. Atropine blocks the muscarinic effects of acetylcholine, the antagonism between acetylcholine and atropine is of competitive type.

In therapeutic doses, atropine causes bradycardia and increase in rate & depth of respiration. Toxic doses of atropine may lead to CNS excitatory effects e.g. restlessness, anxiety, insomnia, delusions and hallucinations etc.

Atropine relaxes the smooth muscles of bronchi and bronchioles which results in widening of the airways. Atropine also cause of retention of urine. Atropine reduces the various body secretions e.g. sweat, salivary, bronchial and lacrimal etc. Atropine produces mydriasis in the eye. It also produces paralysis of accommodation or **cycloplegia** (the condition in which, one can see things clearly only at a long distance and can not constrict the pupil for viewing the near objects clearly). The important therapeutic uses of atropine are as follows:

- Gastrointestinal colic (as antispasmodic)
- CNS disorders
- In organophosphorus poisoning.
- Used for counteracting bradycardia and partial heart block in some patients of myocardial infarction.
- As mydriatic and cycloplegic agent

3.3.2 Semisynthetic and Synthetic Antimuscarinics

Used in eye and onset of mydriasis and cycloplegia is similar to that of atropine but homatropine is not much used for producing cycloplegia.

Cyclopentolate

It is more potent and rapidly acting as compared to homatropine for producing mydriasis and cycloplegia especially in children. It is also used in iritis.

Tropicamide

It is used for refraction testing in adults and as mydriating agent for fundoscopy. It has quickest and briefest action.

Ipratropium Bromide

It is a valuable drug used in the treatment of chronic obstructive pulmonary disease (COPD) by inhalation route. **Titropium bromide** is congener of ipratropium bromide producing long lasting bronchodilatation.

Glycopyrrolate

Rapidly acting antimuscarinic agent and lacking central effects. Used for preanaesthetic medication.

SAQ 1

a) Cholinesterase hydrolyses acetylcholine into _____ and _____.

b) _____ is generally used as a preanesthetic medication.

c) _____ is a drug of choice in the treatment of myasthenia gravis.

d) Acetylcholine exerts its physiological actions by acting on _____ and _____ receptors.

3.4 ADRENERGIC AND ANTIADRENERGIC AGENTS

3.4.1 Adrenergic Agents (Sympathomimetic)

The sympathomimetic or adrenergic or adrenomimetic drugs mimic the effects of adrenergic sympathetic nerve stimulation. These are the important group of therapeutic agents which may be used to maintain blood pressure and in certain cases treatment of severe bronchial asthma.

The action of adrenergic drugs are mediated through interaction with the adrenergic receptors which are broadly classified into the alpha and the beta subtypes. In most of the tissues, the alpha receptor stimulation produces excitatory effect and beta receptor stimulation usually produces inhibitory effect.

Adrenergic drugs can also be classified into:

a) **Direct sympathomimetics:** These act directly on α or/and β adrenoceptors e.g. adrenaline, noradrenaline, isoprenaline, phenylephrine, methoxamine, salbutamol etc.

b) **Indirect sympathomimetics:** They act on adrenergic neurones to release noradrenaline e.g. tyramine.

c) **Mixed action sympathomimetics:** They act directly as well as indirectly e.g. ephedrine, amphetamine, mephentermine etc.

The actions of **Sympathomimetic** drugs on the body (particularly adrenaline and noradrenaline) are as follows:

Heart: Adrenaline increases the heart rate, force of myocardial contraction and cardiac output.

Blood vessels: Adrenaline and noradrenaline constrict the blood vessels of skin and mucous membranes.

Blood pressure: Because of vasoconstriction and vasodilatatory actions of adrenaline, the net result is decrease in total peripheral resistance.

Noradrenaline causes rise in systolic, diastolic and mean blood pressure and does not cause vasodilatation and increase in peripheral resistance due to its α action.

Isoprenaline causes rise in systolic blood pressure but marked fall in diastolic blood pressure but mean blood pressure generally falls.

GIT: Adrenaline causes relaxation of smooth muscles of GIT and reduces its motility. It decreases the tone, frequency and amplitude of contraction of smooth muscles.

Respiratory system: It causes bronchodilatation. Among catecholamines, adrenaline and isoprenaline are potent bronchodilators but not noradrenaline.

Uterus: In human beings, non-pregnant uterus is contracted while pregnant uterus is relaxed in the last month of pregnancy.

Eye: Mydriasis occur due to contraction of radial muscles of iris, intraocular tension is lowered due to less production of the aqueous humor secondary to vasoconstriction and conjunctival ischemia due to constriction of conjunctival blood vessels.

Urinary bladder: The actions tend to inhibit micturition and leads to urinary retention.

The main therapeutic uses of these drugs are in the treatment of:

- Allergic reaction
- Bronchial asthma
- Cardiac uses: Isoprenaline or orciprenaline may be used for the temporary treatment of partial or complete AV block.
- Vascular uses: Pressor agents like adrenaline (more appropriate dopamine or dobutamine) may be useful in hypotensive crisis.
- Adrenaline along with local anaesthetics may be used for infiltration, nerve block and spinal anaesthesia .
- Adrenaline may be useful in control of haemorrhage from the skin and mucous mem-brane such as epistaxis and after tooth extraction.
- Used as nasal decongestant.

Dopamine

It is an immediate metabolic precursor of nor-adrenaline. It causes vasodilatation. It acts on dopaminergic and other adrenergic receptors. It is indicated in shock syndrome due to trauma, septicaemia, heart surgery, renal failure and chronic cardiac failure. Dobutamine is a derivative of dopamine. It increases the force of myocardial contraction and cardiac output without significant change in heart rate, blood pressure and peripheral resistance. It is used as inotropic agent and for short term management of chf and also in patients who are unresponsive to digitalis.

Ephedrine

Ephedrine is an alkaloid obtained from '*Ephedra vulgaris*' plant. It increases blood pressure both by peripheral vasoconstriction and by increasing the cardiac output. Ephedrine also relaxes the bronchial smooth muscles. Ephedrine is **useful** for the treatment of chronic and moderate type of bronchial asthma, used as nasal decongestant and as a mydriatic without producing cycloplegia.

Oxymetazoline

It is used as nasal decongestant in allergic rhinitis, with or without the addition of antazoline or sodium chromoglycate.

Isoprenaline

It is beta-receptor stimulant, which stimulates the heart and causes tachycardia. It relaxes the smooth muscles particularly the bronchial and GIT. It is mainly used in bronchial asthma, in the treatment of shock and as a cardiac stimulant in heart block.

Amphetamine

Amphetamine is a potent CNS stimulant and causes alertness, insomnia, increased concentration, euphoria or dysphoria and increased work capacity. Amphetamine produces wakefulness and improved physical performance. Amphetamines are **drugs of abuse** and can produce behavioral abnormalities and can precipitate psychosis. It can produce psychological but no physical dependence.

Phenylephrine

It is a vasopressor agent with some structural similarity to adrenaline and has a powerful α receptor stimulant action. It is used as a nasal decongestant and mydriatic agent and also in the treatment of paroxysmal supraventricular tachycardia.

Uterine Relaxants (Tocolytics)

These are the agents which decrease uterine motility and have been used to delay or postpone labour and to arrest threatened abortion which is needed to

allow fetus to mature. Isosuprine has beta receptor stimulant action and is used in the treatment of peripheral vascular diseases also. Ritodrine is preferred to suppress premature labour and delay delivery of fetus.

3.4.2 Adrenergic Blocking Agents (Sympatholytics)

These are the agents, which block the action of adrenaline and noradrenaline. They block either alpha or beta or both adrenergic receptors.

3.4.3 Alpha Adrenergic Blockers

Alpha blockers are the drugs which block the pressor response to noradrenaline and convert adrenaline induced stimulation response to depressor response. Blockage of vasoconstrictor receptors reduces peripheral resistance, venous return and cardiac output leading to fall in blood pressure.

Certain stimulant actions of catecholamines on various smooth muscles are blocked by alpha blockers. Alpha blockers can inhibit ejaculation and produce impotence. Salivary secretion and sweat formation induced by catecholamines is blocked by alpha blockers. Miosis and nasal stuffiness can occur with alpha blockers by acting on radial muscles of iris and nasal blood vessels.

Phenoxybenzamine

It is a potent alpha-adrenergic blocking agent and only haloalkylamine used clinically. It is used in the management of pheochromocytoma and also to treat peripheral vasospastic conditions e.g. Raynaud's disease and shock syndrome.

Phentolamine

This alpha blocker is exclusively used for the diagnosis of pheochromocytoma and for the prevention of abrupt rise in blood pressure during surgical removal of adrenal medulla tumors.

Erectile dysfunction:

It is disease in which male human does not produce erection in his genital organ.

Ergot Alkaloids

Ergot is a parasitic fungus (*Claviceps purpurea*). It contains different alkaloids of complex chemical structure. The amino acid ergot alkaloids are ergotamine, ergocristine, ergocornine, ergosine, ergocryptine and their dehydrogenated derivatives can block the alpha receptors. Both ergotamine and dihydroergotamine are used in the treatment of migraine.

Prazosin

It is effective in the management of hypertension. It is used in essential hypertension, benign prostatic hypertrophy and in Raynaud's syndrome.

Yohimbine

It is an alkaloid obtained from an African plant. It produces increase in heart rate and blood pressure due to increase in noradrenaline release. It does not have any use in clinical practice.

The main therapeutic uses of alpha adrenergic blockers are as follows:

- Diagnosis and treatment of pheochromocytoma
- Hypertension
- Congestive heart failure
- Peripheral vascular disease:
- Alpha blockers can be used in secondary shock due to any blood/fluid loss accompanied by reflex vasoconstriction.
- Benign prostate hypertrophy
- Migraine
- Erectile dysfunction

Other drugs used for erectile dysfunction

Sildenafil: It is orally active selective inhibitor of phosphodiesterase type 5 useful in treatment of erectile dysfunction. It is **useful** in erectile dysfunction of any etiology. The newer drugs of same category are **alprostadil, vardenafil** and **tadalafil** which are recently introduced for erectile dysfunction in man.

3.4.4 Beta Adrenergic Blockers

These are the agents which block the action of sympathetic nerve stimulation and circulating sympathomimetic amines on the beta adrenergic receptors. This decreases the rate and force of myocardial contraction of the heart, and decreases the rate of conduction of impulses through the conduction system.

Propranolol

Propranolol is a nonselective beta blocker. The main therapeutic uses of propranolol are as follows:

- Hypertension
- Glaucoma
- Migraine
- Hyperthyroidism
- Angina pectoris
- Myocardial infarction
- Anxiety
- Cardiac arrhythmias
- Pheochromocytoma
- Hypertrophic obstructive cardiomyopathy

Other Beta Blockers

Sotalol

It is nonselective blocking agent with lower lipid solubility with additional potassium channel blocking activity.

Nadolol

It is another nonselective beta blocker with longer duration of action and mainly used in hypertension.

Timolol

It is nonselective agent with no local anaesthetic activity and having excellent ocular hypotensive effect preferred for ophthalmic use. It is useful in chronic wide-angle and acute angel glaucoma.

Pindolol

It is a nonselective beta blocker with marked intrinsic sympathomimetic activity. It has advantage over propranolol that it produces less bradycardia and rebound hypertension.

Cardioselective/β_1 Blockers

Metoprolol

It is cardioselective beta blocking agent and is devoid of intrinsic sympathomimetic activity. Metoprolol may be preferred to a nonselective agent in asthmatics and patients prone to develop hypoglycemia.

Atenolol

It is cardioselective beta blocking agent with low lipid solubility, generally administered once daily because of its longer duration of action. Most commonly used in hypertension and angina pectoris.

Celiprolol

It is cardioselective beta blocker with a modest capacity to activate β_2 receptors also. It is used in treating hypertension and angina pectoris.

The main therapeutic uses of beta blockers are as follows:

Hypertension, ischemic heart disease, angina pectoris, cardiac arrhythmias, hypertrophic cardiomyopathy, congestive heart failure, myocardial infarction, pheochromocytoma, hyperthyroidism, neurologic diseases: Migraine, anxiety, essential tremor and glaucoma.

SAQ 2

a) Naphazoline is used as a _____.

b) _____ is the prototype orally active selective inhibitor of phosphodiesterase type 5 useful in treatment of erectile dysfunction.

c) Phenoxybenzamine produces _____ block of the alpha adrenergic receptors.

d) Prazosin is an example of a selective _____ blocker.

3.5 SUMMARY

- Cholinergic agents are drugs which stimulate the parasympathetic system and mimic the action of acetylcholine.
- Anticholinesterases are the drugs which act by inhibiting the enzymes true and pseudocholinesterase and thereby produce an accumulation of acetylcholine at the various cholinergic sites.
- Anticholinergic or cholinergic blocking agents are the agents which block the action of acetylcholine at the postganglionic parasympathetic nerve endings. They are also termed as antimuscarinic or muscarinic blockers.
- Atropine is the drug of choice in organophosphorous poisoning.
- The sympathomimetic or adrenergic or adrenomimetic drugs mimic the effects of adrenergic sympathetic nerve stimulation.
- The catecholamines produce their action by direct combination with alpha and beta receptors located on the cell membrane.
- Ritodrine is a β_2 selective agonist with uterine relaxant property. It is the preferred drug for suppression of premature labour.

3.6 TERMINAL QUESTIONS

1. What are the physiological actions of Ach on the heart?
2. Classify the irreversible anticholinesterases.
3. What are the physiological actions of adrenaline on the body?
4. What are the therapeutic uses of beta blockers?

3.7 ANSWERS

Self Assessment Questions 1

1. a) Choline and acetic acid b) Glycopyrrolate c) Neostigmine d) Muscarinic and Nicotinic.
2. a) Nasal decongestant b) Sildenafil c) Cardioselective beta blockers

Terminal Questions

1. Acetylcholine decreases the contractility (negative inotropy) and decreases the conduction velocity of the atria. It decreases the heart rate (negative chronotropy) and may cause cardiac arrest. Acetylcholine dilates all blood vessels causing flushing and fall in blood pressure.

2. The organophosphorus cholinesterase inhibitors like diisopropyl fluorophosphate, phospholine, parathion, malathion etc. are highly toxic compound and cause irreversible inhibition of both true and pseudo cholinesterase. They are highly lipid soluble compound and can easily cross the blood-brain barrier.

3. **Cardiovascular system:** Adrenaline increases the heart rate, force of myocardial contraction and cardiac output. The blood vessels of skin and mucous membranes are constricted.

   GIT: Adrenaline causes relaxation of smooth muscles of GIT and reduce its motility. It decreases the tone, frequency and amplitude of contraction of smooth muscles.

   Respiratory system: It causes bronchodilatation. Among catecholamines, adrenaline and isoprenaline are potent bronchodilators but not noradrenaline

   Uterus: In human beings, non-pregnant uterus is contracted while pregnant uterus is relaxed in the last month of pregnancy.

   Eye: Mydriasis occur due to contraction of radial muscles of iris, intraocular tension is lowered due to less production of the aqueous humor secondary to vasoconstriction and conjunctival ischemia due to constriction of conjunctival blood vessels.

   Urinary bladder: The actions tend to inhibit micturition and leads to urinary retention.

4. The main therapeutic uses of beta blockers are as follows: Hypertension, Glaucoma, Migraine, Hyperthyroidism, Angina pectoris, Myocardial infarction, Anxiety, Cardiac arrhythmias and Pheochromocytoma.