Chapter ... 10

# PARASYMPATHOLYTICS

## ♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- ❖ Describe the pharmacodynamic properties of parasympatholytics
- ❖ Identify major adverse effects and clinical uses of parasympatholytic drugs

## 10.1 INTRODUCTION

Parasympatholytic or anticholinergic agents block or inhibit the action of cholinergic agents or endogenous acetylcholine at the post ganglionic nerve endings by blocking cholinergic receptor of parasympathetic nerves and inhibit its activity. These drugs are also called Parasympathetic blockers or anticholinergic or cholinergic blocking agents. They block the muscarinic receptor actions of acetylcholine and related drugs hence also called as antimuscarinic agents. The drug or substances have ability to inhibit the activity of parasympathetic nervous system by blocking cholinergic receptor at the post ganglionic nerve ending. The parasympathetic or cholinergic blocking agents include atropine, and related alkaloids obtained from the plant *Atropa belladonna*, *Atropa acuminate*, *Hyoscyamus niger*, *Scopola carniolica* and *Datura stramonium*. These drugs in therapeutic doses predominatly block the muscarinic actions of acetylcholine; the ganglionic and skeletal neuromuscular actions of acetylcholine are not affected.

Anticholinergics are used for asthma, COPD, diarrhoea, nausea, vomiting, Parkinson's dise ase and to decrease smooth muscle spasms (e.g., in the urinary bladder).

## 10.2 CLASSIFICATION

1. **Natural alkaloids:** Atropine, Scopolamine.
2. **Semisynthetic derivatives:** Homatropine, Atropine methonitrate, Hyoscine butyl bromide, Ipratropium bromide, Tiotropium bromide.
3. **Synthetic compounds:**
   (a) **Mydriatics:** Cyclopentolate, Tropicamide.

(b) **Antisecretory-antispasmodics:** Propantheline, Oxyphenonium, Clidinium, Pipenzolate methylbromide, Isopropamide, Glycopyrolate, Dicyclomine, Oxybutynin, Flevoxate, Pirenzepine, Telenzepine.

(c) **Antiparkinsonian:** Trihexyphenidyl, Procyclidine, Biperiden, Benztropine, Cycrimine, Ethopropazine.

**Classification on the basis of mode of action:**

1. **Non-selective muscarinic receptor antagonists:** Atropine, Scopolamine, Homatropine.
2. **Selective muscarinic receptor antagonists:**
   (a) **$M_1$ antagonists:** Pirenzepine, Telenzepine, Trihexypheridyl.
   (b) **$M_2$ antagonists:** Methoctramine.
   (c) **$M_3$ antagonists:** Hexahydrosiladefenidol, 4-DAMP.
   (d) **$M_4$ antagonists:** Himbacine.

## 10.3 SOURCES AND CHEMISTRY OF ANTICHOLINERGIC DRUGS

Atropine is obtained from *Atropa belladonna*, and *Datura stramonium*. Scopolamine is found in the shrub *Hyoscyamus niger* and *Scopolia carniolica*. Atropine consists of equal parts of d-and 1-hyoscyamine, but the antimuscarinic activity is almost wholly due to the 1-isomer. The active ingredient in scopolamine is 1-hyoscine. Atropine (hyoscyamine) is composed of tropic acid (active) and tropine (tropanol-inactive).

Scopolamine (hyoscine) is the structural combination of tropic acid (active) and scopine (inactive). Homatropine is the combination of mandelic acid and tropine. The intact ester of tropine or scopine and tropic or mandelic acid is essential for the significant anti-muscarinic action of these drugs. The free OH group in the acid portion is also important.

**Mechanism of Action:**

Atropine and related drugs are competitive antagonists of ACh and other muscarinic agonists. They compete with such agonists for a common binding site on the muscarinic receptor. The receptors affected are those of exocrine glands and smooth and cardiac muscles.

Muscarinic receptors in ganglia and on intramural neurons are also affected. In extremely high non-therapeutic doses, atropine can also block the nicotinic receptors of autonomic ganglia and the motor end-plate of skeletal muscles; however, these sites are not affected with ordinary doses.

**Pharmacological Action:**

***(i) Cardiovascular System:***

- Atropine initially produces bradycardia, a central action (increase in vagal activity).
- Slightly larger doses of it produce tachycardia due to $M_2$ receptor blockade. Cardiac output is also increased.
- Low doses of scopolamine produce more marked slowing of heart rate than that of atropine. High doses accelerate the heart beat which is short lived.
- Atropine-like drugs antagonize the fall in B.P. caused by choline esters.
- Atropine alone cannot affect B.P.

***(ii) CNS:***

- Atropine at therapeutic dose produces minimal effects on CNS (only mild vagal excitation, mild restlessness), but higher doses cause stimulation followed by depression of the CNS.
- Scopolamine in low dose produces depression and in high dose causes excitement and delirium.

***(iii) Smooth Muscle:***

**(a) GIT:**

- Atropine reduces the gastrointestinal motility by preventing the effect of endogenous ACh.
- Atropine and more important Pirenzepine inhibit gastric acid secretion, hence used in the treatment of peptic ulcer.

**(b) Biliary tract:** Atropine exerts a weak antispasmodic action on the biliary tract and gall bladder.

**(c) Urinary tract:** Atropine has been demonstrated to produce reduction in normal as well as drug induced ureteral peristalsis. It does not completely abolish the bladder response to stimulation of the sacral parasympathetic fibres. Therapeutic doses ten to reduce the tone of the fundus of the bladder and enhance the tone of the trigonal sphincter and may cause urinary retention.

**(d) Bronchi:** Atropine relaxes the smooth muscles of the bronchi and bronchioles. It is particularly effective in relieving bronchoconstriction produced by cholinergic agents but is much less potent than adrenaline in relieving histamine induced bronchoconstriction. Since, it dries up the secretions, it is not recommended in the treatment of bronchial asthma.

**(e) Uterus:** Atropine and Scopolamine have no significant effect on the tone and motility of the uterine smooth muscle.

***(iv) Glands:***

- Atropine markedly decreases sweat, salivary, tracheobronchial and lacrymal secretions.

***(v) Smooth Muscles:***

- Atropine relaxes GIT, bronchial, biliary and urinary tract smooth muscles.

***(vi) Eye:***

- Mydriasis and cycloplegia due to blockade of muscarinic receptors on circular muscle of iris and ciliary muscle respectively.

***(vii) Other effects:***

- Increase in body temperature (atropine fever).
- Atropine has a mild anaesthetic action on the cornea.

**Pharmacokinetic:** The belladonna alkaloids are satisfactorily absorbed from the gastrointestinal tract, from parenteral sites of administrations and from mucous membranes. The absorption from the eye and intact unbroken skin however is no significant. Atropine is partly detoxified in liver and partly excreted unchanged by kidneys. Approximately 50% of parenterally administered drug appears in the urine in free form with 24 hours while 33% is excreted as unknown metabolites.

Atropine crosses the placental barrier and is secreted in milk and saliva. Some rabbits possess the enzyme atropine esterase in the plasma and the liver and are able to detoxify atropine much more rapidly than human beings.

**Adverse reaction:** Dry mouth, blurry vision, constipation, Drowsiness, Sedation, hallucinations, memory problems, trouble urinating, confusion, delirium, decreased sweating, and decreased saliva. Atropine can precipitate glaucoma in elderly persons; locally atropine can give rise to allergic reactions such as dermatitis, conjunctivitis and swelling of eyelids.

**Clinical Uses of Anti-Muscarinic Agents:**

- As **spasmolytic** to decrease hyper-motility of GIT and hyper-tonicity of the uterus, urinary bladder, ureter, bile ducts and bronchioles.
- Hyoscine (Scopolamine) Hydrobromide in the dose of 0.5 to 1 mg by mouth is used in the treatment of **motion sickness**.
- As **preanesthetic** to inhibit excessive salivation and respiratory secretions. e.g. atropine (Dogs-0.045 mg/kg b.wt., s.c. inj.)
- In **peptic ulcer** – Pirenzepine.
- To **dilate the pupil:** Homatropine 2-5% sol. Tropic amide eye drops (short acting) and Cyclopentolate eye drops (long acting) are more commonly used.
- In **renal colic** – Atropine and an opioid.
- In **bronchial asthma** – Ipratropium by inhalation.
- In organophosphates, carbamate and mushroom **poisoning** - Atropine sulphate (all animals- 0.2-0.5 mg/kg b.wt., 1/4$^{th}$ i.v. inj. and 3/4$^{th}$ i.m. inj., at 3-6 hours intervals).
- To **antagonize** the toxic effects of neostigmine (administered in myasthenia gravis).
- In **Parkinsonism**, Central anticholinergics are less effective than levodopa; they are used in mild cases, in drug induced extrapyramidal syndromes and as adjuvant to levodopa.

**Ipratropium bromide:** Ipratropium bromide is a bronchodilator that dilates airways (bronchi) in the lungs. It is used in treating, symptoms of asthma, colds, allergies and chronic obstructive pulmonary disease (COPD) due to emphysema or chronic bronchitis. Ipratropium blocks the effect of acetylcholine on airways (bronchi) and nasal passages. In asthma and chronic obstructive pulmonary disease, cholinergic nerves going to the lungs cause narrowing of the airways by stimulating muscles surrounding the airways to contract. The "anti-cholinergic" effect of ipratropium blocks the effect of cholinergic nerves, causing the muscles to relax and airways to dilate. Mucus glands in the nose also are controlled by nerves that use acetylcholine to communicate. By blocking acetylcholine, ipratropium helps to

relieve symptoms of allergies and the common cold by preventing secretion of mucus by mucus glands in the nose. When inhaled, ipratropium travels directly to airways, and very little is absorbed into the body.

**Side Effect:** Dry mouth, cough, headache, nausea, dizziness, and difficulty breathing.

Ipratropium can cause bronchospasms that can be life-threatening. It can also cause rash, itching, or serious allergic reactions involving closure of the airways.

Because of its anticholinergic effect it may worsen symptoms of benign prostatic hyperplasia and narrow-angle glaucoma.

**Preparations and Dosage:**

- The recommended dose for allergies is 2 sprays (0.03%) in each nostril 2 or 3 times daily. (Ipranase-AQ 0.084% nasal spray).
- The dose for treating symptoms of the common cold is 2 sprays (0.06%) in each nostril 3 to 4 times daily.
- The dose for treating asthma is 8 inhalations every 20 minutes as needed for up to 3 hours.
- The dose for treating bronchospasms associated with COPD is 2 puffs 4 times daily and additional puffs if needed but not to exceed 12 puffs per day. (Ipravent 20 µg/Puff metered dose inhaler).

**Tiotropium bromide:** A recently developed conger of Ipratropium bromide which binds very tightly to bronchial Muscarinic receptors producing long lasting bronchodilation.

**Propantheline bromide:** Propantheline is an anticholinergic drug, a medication that reduces the effect of acetylcholine, a chemical released from nerves that stimulates muscles, by blocking the receptors for acetylcholine on smooth muscle (a type of muscle). It also has a direct relaxing effect on smooth muscle. Propantheline is used to treat or prevent spasm in the muscles of the gastrointestinal tract in the irritable bowel syndrome. In addition, Propantheline inhibits gastrointestinal propulsive motility and decreases gastric acid secretion and controls excessive pharyngeal, tracheal and bronchial secretions. 15-30 mg oral; has been most popular anticholinergic used for peptic ulcer and gastritis. It is claimed to reduce gastric secretion at doses which produce only mild side effects. (Probanthine 15 mg tablet.)

**Oxyphenonium:** 5-10 mg oral; similar to propantheline recommended for peptic ulcer and gastrointestinal hypermotility.

**Dicyclomine:** A muscarinic antagonist used as an antispasmodic and in urinary incontinence. It has little effect on glandular secretion or the cardiovascular system. It does have some local anesthetic properties and is used in gastrointestinal, biliary, and urinary tract spasms. Dicyclomine is an anticholinergic drug, a medication that reduces the effect of acetylcholine, a chemical released from nerves that stimulates muscles, by blocking the receptors for acetylcholine on smooth muscle (a type of muscle). It also has a direct relaxing effect on smooth muscle. Dicyclomine is used to treat or prevent spasm in the muscles of the

gastrointestinal tract in the irritable bowel syndrome. In addition, Dicyclomine inhibits gastrointestinal propulsive motility and decreases gastric acid secretion and controls excessive pharyngeal, tracheal and bronchial secretions. It also has antiemetic property, has been used in morning sickness and motion sickness. Dysmenorrhea and irritable bowel syndrome are other indications. Cyclopam 10 mg in 2 ml, 10 ml, 30 ml amp/vial, also 20 mg tab with paracetamol 500 mg.

**Oxybutynin:** Oxybutynin reduces muscle spasms of the bladder and urinary tract. Oxybutynin is used to treat symptoms of overactive bladder, such as frequent or urgent urination, incontinence (urine leakage), and increased night-time urination.

**Pirenzepine:** Pirenzepine is an antimuscarinic agent that inhibits gastric secretion at lower doses than are required to affect gastrointestinal motility, salivary, central nervous system, cardiovascular, ocular, and urinary function. It promotes the healing of duodenal ulcers and due to its cytoprotective action is beneficial in the prevention of duodenal ulcer recurrence. It may also be used to prevent nausea, vomiting, and motion sickness. Pirenzepine is a muscarinic receptor antagonist and binds to the muscarinic acetylcholine receptor. The muscarinic acetylcholine receptor mediates various cellular responses, including inhibition of adenylate cyclase, breakdown of phosphoinositides and modulation of potassium channels through the action of G proteins.

**Telenzepine:** Effects are similar to Pirenzepine more potent.

## QUESTIONS

1. What are parasympatholytics agents?
2. Write the therapeutic uses of atropine.
3. Classify parasympatholytics agents with suitable examples.
4. Write the pharmacological account atropine.

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