MUSCARINIC ANTAGONISTS

- mAChR antagonists (parasympatholytic drugs)
- They are competitive antagonists whose chemical structures contain ester and basic groups in the same relationship as ACh.
- They have a bulky aromatic group in place of the acetyl group.
- ***Atropine*** and ***hyoscine*** (also known as scopolamine) are alkaloids found in solanaceous plants.
- The deadly nightshade (Atropa belladonna) contains mainly atropine
- The thorn apple (Dhatura stramonium) contains mainly hyoscine

MECHANISM OF ACTION

- These drugs are competitive antagonists of the binding of ACh to muscarinic receptors.

- The seven transmembrane helices of these receptors have a ringlike organization in the forms a narrow central cleft where ACh binds.

- Although the tertiary amine and quaternary ammonium groups of drugs bind to the same anionic site on the activate the receptor.

PHARMACOLOGICAL ACTIONS

- Muscarinic antagonists have no intrinsic activity.
- They can produce effects only by blocking the activation of muscarinic receptors by muscarinic agonists.
- The magnitude of the response produced by muscarinic antagonists depends on the existing level of cholinergic activity.
- The tissues or systems affected will depend on the dose administered and the drug’s pharmacokinetic properties.
- Increased entry into the CNS at higher concentrations), and the differential sensitivity of muscarinic receptors in various organs

Heart

- Intravenous administration of low doses of atropine often produces slight bradycardia

- Higher doses produce tachycardia by directly blocking the para-sympathetic input to the sinoatrial node.

- One explanation for the paradoxical bradycardia produced by low doses is that they block presynaptic autoreceptors

- Atropine can also facilitate atrioventricular conduction and block parasympathetic effects on the cardiac conduction.

Blood Vessels

- Atropine and other muscarinic antagonists produce minimal effects on the circulation in the absence of circulating muscarinic agonists.

- This reflects the relatively minor role of cholinergic innervation in determining vascular smooth muscle tone.

- Atropine can produce flushing in the blush area owing to vasodilation.

- It is not known whether this is a direct effect or a response to the hyperthermia induced by the drug’s ability to inhibit sweating.

Gastrointestinal Tract

- Muscarinic antagonists have numerous effects on the digestive system .

- The inhibition of salivation by low doses of atropine results in a dry mouth and difficulty in swallowing.

- Inhibit gastric acid secretion and gastrointestinal motility, because both processes are partly under the control of the vagus nerve.

- Relatively large doses of atropine are required to inhibit acid secretion.

- Dry mouth, tachycardia and urinary retention are drawbacks to the use of muscarinic antagonists in the treatment of peptic ulcers.

Bladder

- Muscarinic antagonists can cause urinary retention by blocking the excitatory effect of ACh on the detrusor muscle of the bladder.

- During urination, cholinergic input to this smooth muscle is activated by a stretch reflex.

Central Nervous System

- Although atropine and scopolamine share many properties, an important difference is the easier entry of scopolamine into the CNS.

- Typical doses of atropine (0.2–2 mg) have minimal central effects, while larger doses can produce a constellation of responses collectively termed the central anticholinergic syndrome.

- At intermediate doses (2–10 mg), memory and concentration may be impaired, and the patient may be drowsy.

- If doses of 10 mg or more are used, the patient may exhibit confusion, excitement, hallucinations, ataxia and possibly coma.

- Even low doses of scopolamine have central effects.
- Sedation, amnesia, and drowsiness are common during the clinical use of this drug.
- Large doses of scopolamine can produce all of the responses seen with atropine.

Eye

- Atropine block contraction of the iris sphincter and ciliary muscles of the eye produced by ACh.

- This results in dilation of the pupil (mydriasis) and paralysis of accommodation (cycloplegia), responses that cause photophobia and inability to focus on nearby objects.

- Ocular effects are produced only after higher parenteral doses.

- Atropine and scopolamine produce responses lasting several days when applied directly to the eyes.

Lung

- Muscarinic antagonists inhibit secretions and relax smooth muscle in the respiratory system.
- The parasympathetic innervation of respiratory smooth muscle is most abundant in large airways, where it exerts a dominant constrictor action.
- Therefore muscarinic antagonists produce their greatest bronchodilator effect at large-caliber airways.
- By this mechanism they can block reflex laryngospasm during surgery.
- In addition, these drugs are potent inhibitors of secretions throughout the respiratory system, from the nose to the bronchioles.

Clinical uses

Cardiovascular Uses

- Atropine can be useful in patients with carotid sinus syncope.
- This condition results from excessive activity of afferent neurons whose stretch receptors are in the carotid sinus.
- By reflex mechanisms, this excessive afferent input to the medulla oblongata causes pronounced bradycardia, which is reversible by atropine.

- Atropine can be used in the differential diagnosis of S-A node dysfunction.

- If sinus bradycardia is due to extracardiac causes, atropine can generally elicit a tachycardic response,

- It cannot elicit tachycardia if the bradycardia results from intrinsic causes

- Atropine can also be used to induce positive chronotropy during cardiopulmonary resuscitation.

Uses in Anesthesiology

- atropine or scopolamine was routinely administered before the induction of general anesthesia to block excessive salivary and respiratory secretions

- With the newer, less irritating anesthetics, antimuscarinic premedication is not routinely required as an antisialagogue .

- Glycopyrrolate bromide has also been given intramuscularly as a preanesthetic medication with satisfactory results.

- This agent is a quaternary ammonium compound and therefore produces no central effects.

Uses in Ophthalmology

- Muscarinic antagonists are widely used in ophthalmology to produce mydriasis and cycloplegia.

- These actions permit an accurate determination of the refractive state of the eye, and also useful in treating specific ocular diseases and following iridectomy.

- Atropine, scopolamine, cyclopentolate and tropicamide are among the agents used in ophthalmology.

- All of these agents are tertiary amines that reach the iris and ciliary body after topical application to the eye.

- Systemic absorption from the conjunctival sac is minimal, but significant absorption and toxicity can occur if the drugs come into contact with the nasal and pharyngeal mucosa via the nasolacrimal duct.

- To minimize this possibility, pressure should be applied to the lacrimal sac for a few minutes after topical application of muscarinic blockers.

- The actions of atropine and scopolamine can persist for a week after topical application to the eye.

- Shorter-acting drugs, such as cyclopentolate and tropicamide, are now favored for this application because complete recovery of accommodation occurs within 6 hours.

Uses in Disorders of the Digestive System

- Pirenzepine and telenzepine have been employed in the therapy of peptic ulcers because they can reduce gastric acid secretion; they also have been used as adjunctive therapy in the treatment of irritable bowel syndrome.

- They can decrease the pain associated with postprandial spasm of intestinal smooth muscle by blocking contractile responses to ACh.

- Some of the agents used for this disorder have only antimuscarinic activity (e.g., propantheline), while other drugs have additional properties that contribute to their antispasmodic action.

- Dicyclomine and oxybutynin at therapeutic concentrations primarily have a direct smooth muscle relaxant effect with little antimuscarinic action.

Uses in Urology

- Propantheline , oxybutynin, dicyclomine, and several other agents have been used for uninhibited bladder syndrome, bladder spasm, enuresis, and urge incontinence.

- Tolterodine a nonselective muscarinic antagonist, exhibits functional specificity for blocking muscarinic receptors in the bladder, with fewer side effects than oxybutynin.

Uses in Respiratory Disorders

- For a long time, muscarinic receptor–blocking drugs oc- cupied a major place in the therapy of asthma.

- Ipratropium bromide is a synthetic muscarinic blocking drug that has gained widespread use in recent years

- The drug is a quaternary ammonium compound, and it is applied topically to the airways through the use of a metered-dose inhaler.

- Dryness of the mouth, cough, and a bad taste have been reported by some patients, but the drug appears to have no other significant adverse effects.

- Ipratropium does not affect mucociliary transport or the volume and viscosity of sputum.

Parkinsonism

- Although therapy of Parkinson's disease is directed toward replacement of the dopaminergic deficiency rather than blocking the cholinergic excess

- Muscarinic antagonists are sometimes employed for mild cases and in combination with other agents (e.g., levodopa) for treatment of advanced cases.

- Benztropine and trihexyphenidyl are preferred agents

Motion Sickness

- Scopolamine is useful for prevention of motion sickness when the motion is very stressful and of short duration.
- A transdermal preparation with a 72-hour duration of action has been marketed for this purpose.
- Blockade of cholinergic sites in the vestibular nuclei and reticular formation may account for the effectiveness of this agent.

Cholinomimetic Poisoning

- Atropine is used as an antidote in poisoning by an over-dose of a cholinesterase inhibitor like organophosphate .
- It also is used in cases of poisoning from species of mushroom that contain high concentrations of muscarine and related alkaloids (e.g., Clitocybe dealbata).