Cholinoceptor Antagonists

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Abstract

Ever since the first documented use of the first prototypical anticholinergic drug, atropine in 1554 as mydriatic, modern science has discovered and invented a series of anticholinergic drugs. A detailed study of the structure–activity relationship led to the development of tertiary and quaternary compounds with different pharmacokinetic properties. Antimuscarinic compounds are commonly used as antidotes in OPC poisoning, mydriatics, spasmolytics, COPD, asthma, sedatives, counteract the acute dystonia, and others. On the otherhand, antinicotinic drugs are frequently used as skeletal muscle relaxants. Antimuscarinic agent produces its characteristics side effects like dry mouth, loss of accommodation, urinary retention, and tachycardia owing to the muscarinic receptor blockade. The majority of these side effects are exploited for certain clinical conditions (urinary retention for hyperactive bladder, tachycardia for sick sinus syndrome, among others). This chapter will review in detail the SAR, action, side effects, and clinical uses of antimuscarinic compounds.

Keywords

Atropine · Anticholinergic drugs · Mydriatics · Antimuscarinic drugs · Ganglion blockers

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2.1 Introduction

In 1554, an Italian botanist Pietro A. Mattiolli made a remarkable commentary in "De material Medica" about the use of *Atropa belladonna* extract to cause mydriasis in Italian young women for appealing appearances. It became the first documented use of anticholinergic drugs in the history of medicine. The name *Atropa belladonna* was given to the poisonous "Deadly Nightshade" plant based on this historical use (*bella—beautiful; donna—woman*). The term "Atropa" is derived after the Atropos (the oldest sister in the God of Fate who cuts the thread of life in Greek Mythology) that indicates the toxicological significance of *Atropa belladonna*. In India, smoke from the burnt leaves and roots of *Datura stramonium* (Jimson weed) was used to treat asthma by ancient Hindus and saints. Both these plants contain a natural antimuscarinic alkaloid—atropine.

Even before identifying the active antimuscarinic alkaloids in plants, humans have used it as drug and recorded its effects in the human body for centuries. Only in 1831, the first alkaloid of antimuscarinic group—atropine—was isolated successfully by Mein. Later, the pharmacological actions of atropine were documented and after careful analysis of its structure, various semisynthetic and synthetic antimuscarinic drugs were invented. In the current era, anticholinergic drugs play a vital role in the management of various diseases.

By convention, anticholinergic drugs represent "antimuscarinic" drugs. Antinicotinic drugs are called "ganglion blockers" and "peripheral skeletal muscle relaxants." Ganglion blockers were used as antihypertensive drugs but nowadays they are obsolete and only of toxicological interest.

2.2 Classification

- Antimuscarinic drugs can be classified in two ways. First, based on their source and derivation, antimuscarinic drugs are divided into natural alkaloids, semisynthetic, and synthetic.
- Second, based on their clinical application and therapeutic uses, antimuscarinic drugs are classified into mydriatics, spasmolytics, central anticholinergics, vasicoselectives, bronchodilators, and non-selective antimuscarinic agents. Both the classifications of antimuscarinic drugs are illustrated in Fig. 2.1.

2.3 Chemistry and Structure–Activity Relationship

- The natural alkaloids of antimuscarinic drugs are the esters of tropic acid (3-OH phenyl propionic acid) with an organic base (scopine or tropine). The basic representation of structure of any antimuscarinic agent is illustrated in Fig. 2.2. Homatropine differs from atropine by the presence of mandelic acid instead of

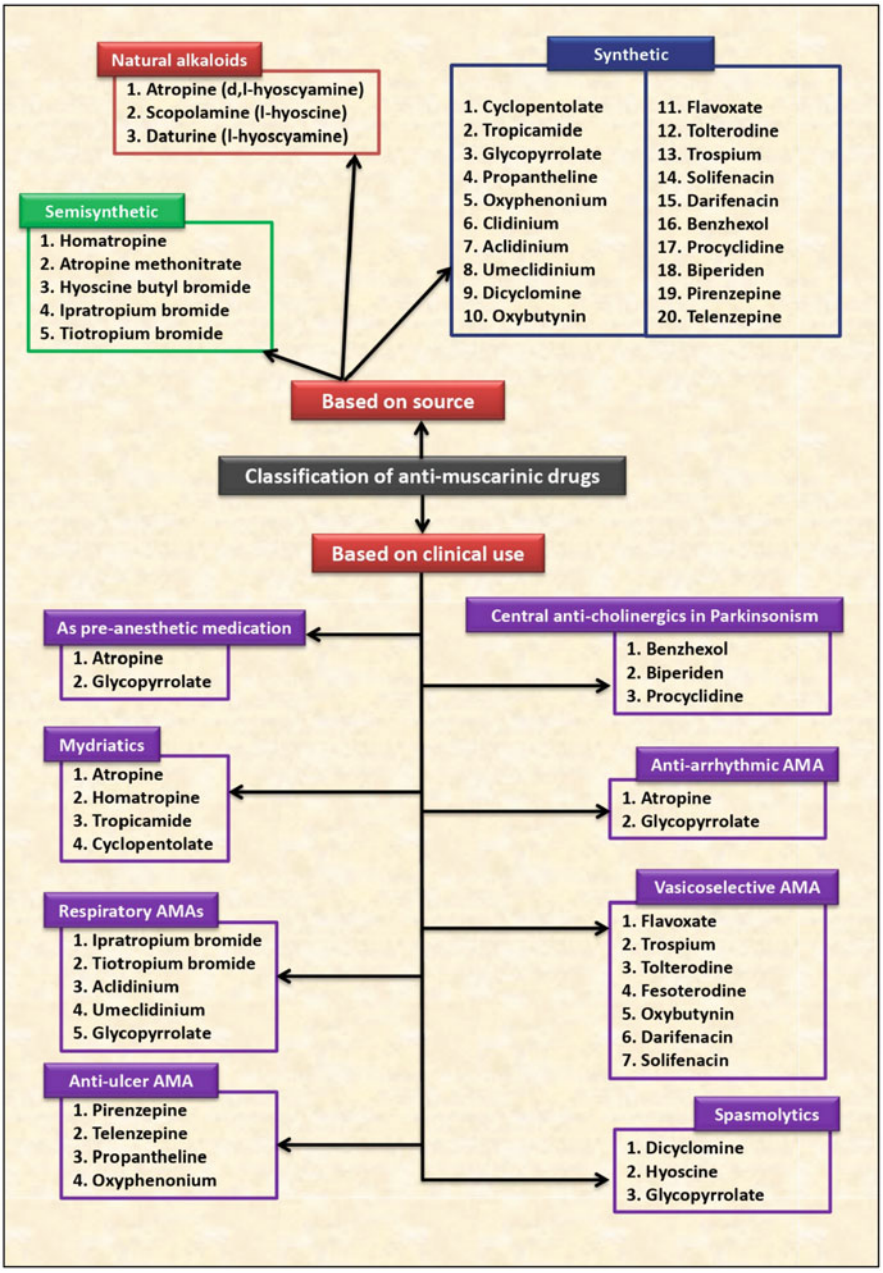

Fig. 2.1 Classification of antimuscarinic drugs

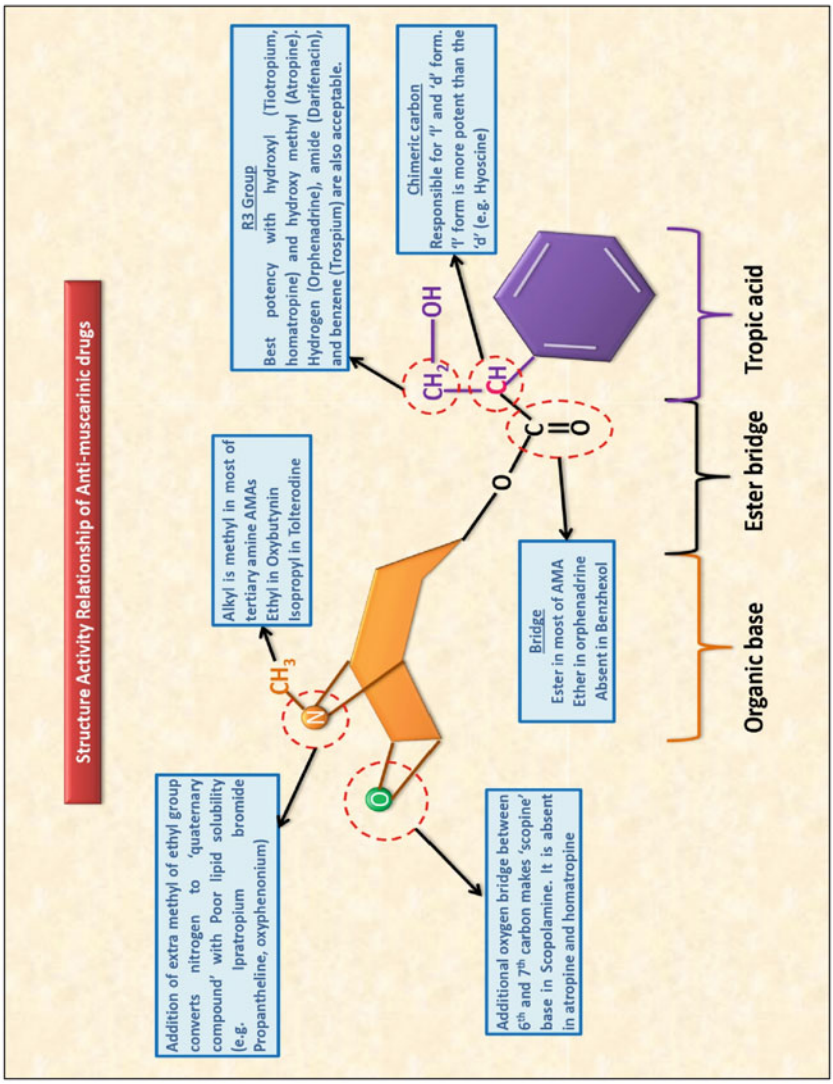

Fig. 2.2 Structure–activity relationship of antimuscarinic drugs

tropic acid in atropine. Scopolamine differs from atropine by the presence of scopine base instead of tropine. Scopine contains an extra oxygen bridge C6 and C7 in tropine structure.

- Substitution of methyl or ethyl group in the nitrogen atom of the organic base converts it into "quaternary ammonium" compounds. These anticholinergic drugs poorly cross BBB and produce less CNS adverse effects (e.g., ipratropium, tiotropium, oxitropium, and glycopyrrolate).
- Enantiomeric center is present in both mandelic and tropic acid resulting in the formation of l- and d- isomer of hyoscine and atropine. l-hyoscine is called as scopolamine and more potent than d-hyoscine. Similarly, the levo-isomer of atropine is called hyoscyamine.
- To exert the antimuscarinic activity, the drug should contain the following:
  - intact ester of tropic/mandelic acid with organic base, and
  - presence of free-OH in the acyl portion of ester.
- The benzene ring in the tropic/mandelic acid can be altered without affecting the antimuscarinic activity. Instead of benzene ring, pyrrolidine group can be substituted (e.g., glycopyrrolate).
- The antimuscarinic potency will be increased if two rings are substituted instead of one ring (like in tropic acid) in the enantiomeric carbon atom (e.g., Trospium).
- The ester bridge is present in most of the potent antimuscarinic drugs. However, it can be replaced with ether (e.g., orphenadrine) or totally removed (e.g., benzhexol).
- The bridge between the nitrogen and enantiomeric carbon can vary from 2 to 4 carbon chain. However molecules with only 2 carbon chain retain potent antimuscarinic activity (e.g., procyclidine, orphenadrine).
- Newer antimuscarinic are selective towards particular receptors and are not determined by the structure–activity relationship.

2.4 Pharmacological Actions

The pharmacological actions of anticholinergic drug vary from organ to organ. The effect of anticholinergic drug noted in each organ depends upon the "dominant" role of parasympathetic system against sympathetic system in that particular organ. Organs like heart, eye, and lungs show major modulation with anticholinergic therapy, while blood vessels, GIT, and CNS show minimal changes.

2.4.1 Central Nervous System

- Scopolamine is ten times more potent than atropine in terms of CNS action.
- Scopolamine causes CNS depressive actions like fatigue, amnesia, drowsiness, and dreamless sleep even at very low doses. Scopolamine also abolishes neural

pathway signals from the vestibular apparatus to emetic center (preferred for motion sickness).

- Conversely, atropine at dose of 0.5–2 mg produces very mild sedation and diminishes memory and attention. Clinical dose of atropine often stimulates parasympathetic medullary centers. Higher dose of atropine (>10 mg) produces CNS excitation and accompanied by vivid hallucination and delirium; even higher doses of more than 200 mg produce coma by CNS depression and death.
- Normal dose of scopolamine in the presence of pain or high dose of scopolamine produces CNS excitation similar to atropine.
- The difference between the atropine and scopolamine in terms of CNS action can be explained by their potency, relative permeability across BBB, and subjective feeling by the patients.

2.4.2 Heart

- Atropine at low dose (0.4–0.6 mg) produces transient bradycardia by blocking the presynaptic M_1 receptor at postganglionic fibers in SA node. Presynaptic M_1 receptors act as "autoreceptors" which decrease ACh release. Blockade of presynaptic M_1 receptors by atropine produces increased ACh release and thereby produces bradycardia.
- Clinical doses of atropine (>0.6 mg) produce tachycardia by blocking the postsynaptic M_2 receptors present in the SA node. Heart rate increases by 35 to 40 bpm owing to the blockade of vagal tone.
- In many clinical situations, atropine fails to produce adequate elevation of heart rate. The following are the factors that affect the "chronotropic effect" produced by atropine:
  - Age (decreased vagal tone in elderly results in less tachycardia).
  - Diabetes (autonomic neuropathy resulting in impaired vagal control).
  - Uremia (decreased sensitivity of pacemaker cells to ACh and impaired vagal function).
  - Digitalis therapy (direct vagomimetic action of digoxin on SA node, AV node, and atrial muscle counteracts atropine).
  - On opioid therapy (central vagal stimulation by the opioids counteracts the effect of atropine on heart).
- Atropine increases the AV nodal conduction and thereby decreases AV nodal delay and PR interval in ECG.
- Atropine does not alter the maximal heart rate achieved by exercise.

2.4.3 Blood Vessels and Blood Pressure

- Atropine does not have significant role in maintenance of BP owing to the fact that blood vessels lack cholinergic supply.

- However, by causing tachycardia, atropine can increase cardiac output and systolic BP. Diastolic blood pressure is not affected at clinical dose of atropine. Mean arterial pressure (MAP) is slightly elevated and it is only due to increased SBP.
- High and toxic dose of atropine produces cutaneous vasodilation, produces flushing (due to histamine release and by direct action), and decreases MAP.

2.4.4 Respiratory System

- By blocking M_3 receptors, atropine and other respiratory anticholinergic drugs produce decreased secretion from the airway glands. Both the mucus secretion and mucociliary clearance are reduced.
- Blockade of post-synaptic M_3 receptors by anticholinergic agents also causes "passive" bronchodilation. In the presence of inflammatory respiratory disorders (like COPD), vagal tone of bronchial wall is significantly increased. Bronchodilation produced by anticholinergic drugs is more in magnitude in COPD than in normal patients. Hence, anticholinergic drugs are very efficacious in such situation by producing bronchodilation.
- Paradoxical bronchoconstriction can occur in anticholinergic therapy due to blockade of presynaptic M_2 receptors.

2.4.5 Eye

- Anticholinergic drugs produce mydriasis in eye by blocking the M_3 receptors present in the sphincter pupillae.
- Cycloplegia is achieved by paralysis of ciliary body by anticholinergic agents. Hence, both light reflex and accommodation are abolished by anticholinergic drugs.
- Insignificant rise in IOT is noted due to narrowing of corneal angle that blocks the trabecular outflow in normal patients. However, anticholinergic can precipitate glaucoma in patients with narrow angle. Thus, anticholinergic drugs should be avoided in patients with predisposition to angle-closure glaucoma.
- Atropine produces mydriasis that lasts for 7–10 days due to ability of atropine to bind with iris pigments and released slowly. Short acting anticholinergic agents like tropicamide are preferred for routine clinical situations. For children and infants with high ciliary tone, atropine is preferred.

2.4.6 Gastrointestinal Tract

- Anticholinergic drugs block M_3 and M_2 receptors in the GI tract and cause partial intestinal relaxation. Motility and peristalsis are decreased but not completely.

- Incomplete effect of anticholinergic drug on GI tract is explained by the fact that vagus has only partial control on GI motility. In GI tract, the non-cholinergic intramural fibers secreting 5-HT, DA, and GRP regulate motility and secretion than vagal mediated ACh. Hence, anticholinergic agents produce partial relaxation in GI tract.
- Acid secretion in the stomach is also partially inhibited by anticholinergic drugs as oxyntic cells receive multiple inputs (histamine, gastrin) besides ACh to secrete HCl.
- The *cephalic phase* of gastric acid secretion is significantly inhibited than that of the *intestinal phase*. This is because in "cephalic phase" vagal mediated ACh plays major role.

2.4.7 Urinary Bladder

- Blockade of both M2 and M3 receptors in the urinary bladder produces detrusor relaxation. Relatively high dose of antimuscarinic drug decreases contraction of ureter and reduces its normal tone and amplitude.

2.4.8 Glands

- Glandular secretions are reduced due to blockade of M_1 and M_3 receptors. Dry mouth, loss of tears, and dry airway ensue with atropine. Salivary glands, sweat glands, and airway glands are highly sensitive than the gastric glands.

2.4.9 Body Temperature

- Normal clinical dose of atropine does not have any significant role in modulation of body temperature.
- At high doses, atropine produces hyperthermia (atropine fever) due to blockade of sweat and stimulation of temperature center in the hypothalamus.

2.5 Individual Drugs

- For ease of understanding, the characteristic features of each drug are compared with the other drugs which are employed for the same therapeutic indication (Tables 2.1, 2.2, 2.3, 2.4, 2.5, and 2.6).

Table 2.1 Comparison of characteristic features of anticholinergic alkaloids

S. No.	Parameter	Atropine	Scopolamine	Homatropine
1	Source	*Atropa belladonna* *Datura stramonium*	*Hyoscyamus niger*	Semisynthetic
2	Other name	l,d-Hyoscyamine	l-hyoscine	Mandelytropine
3	Structure	Tropic acid + tropine	Tropic acid + scopine	Mandelic acid + tropine
4	CNS effect at low dose	Mild excitation (usual) or sedation	Sedation	No data
5	CNS effect at high dose	Excitation	Excitation	Excitation
6	Major indication	Mydriatic in children AV block OPC poisoning Cardiac arrest	Motion sickness	Mydriatic

Table 2.2 Comparison of characteristic features of anticholinergic used as mydriatics

Parameter	Atropine	Homatropine	Tropicamide	Cyclopentolate
Nature	Natural alkaloid	Semisynthetic	Synthetic	Synthetic
Onset of mydriasis	Quick (30–45 min)	Slow (45–60 min)	Quickest (20–30 min)	Quick (30–45 min)
Duration of action	Longest (7–10 days)	Long (1–3 days)	Shortest (3–6 h)	Short (12–24 h)
Cycloplegic effect	Very strong	Strong	Weak	Strong
Potency	High	Low	High	High
Strength (eye drop)	1%	1% and 2%	0.5%, 1%	0.5% & 1%
Choice in children	Yes	No	No	No
Choice in adult	No	Ambivalent	Yes	Yes

2.6 Therapeutic Uses

2.6.1 As Mydriatic and Cycloplegic

- Homatropine, tropicamide, cyclopentolate, and atropine are used as mydriatics and cycloplegic for examination of fundus and testing errors of refraction.
- Short acting drugs like tropicamide and cyclopentolate are preferred for adults in OPD. Atropine is preferred to abolish the high ciliary tone in children to produce effective cycloplegia.
- Atropine is also preferred to abolish pain and spastic miosis caused in uveitis, iridocyclitis, and corneal ulcer.

Table 2.3 Comparison of characteristic features of anticholinergic used as bronchodilators

Parameter	Ipratropium bromide	Tiotropium bromide	Aclidinium bromide	Umeclidinium bromide
Terminology	SAMA	LAMA	LAMA	LAMA
Antagonism	M_1, M_2, and M_3	M_1 and M_3	M_1 M_2 and M_3	M_1 and M_3 $>>$ M_2
Bioavailability after inhalation	1–2%	19.5%	6%	Not known
V_d (by i.v. route)	4.6 L	32 L	300 L	86 L
Protein binding	Very low (0–9%)	High (72%)	Not known	89% (high)
Metabolism	Ester hydrolysis	80% not metabolized; minor 20% by (CYP2D6)	Ester hydrolysis	CYP2D6 with glucuronide conjugation
Onset of action	Fast (<15 min)	<30 min	15–20 min	<15–min
Bronchodilation peaks at	1–2 h	3 h	2 h	1–2 h
Duration of action	4–6 h (short)	24–48 h (long)	12–24 h (long)	24–48 h (long)
Strength and dose	MDI: 34 μg/puff (TDS or QID)	MDI: 2.5 to 5 μg/puff (OD)	DPI: 400 μg/puff (BD)	DPI: 62.5 μg/puff (OD)
Paradoxical bronchoconstriction	Present	No	Occasional	No
Formulation	MDI Nebulizer	MDI and DPI	MDI and DPI	DPI

DPI dry-powder inhaler, *LAMA* long acting muscarinic antagonist, *MDI* metered dose inhaler, *SAMA* short acting muscarinic antagonist

2.6.2 As Spasmolytics

- Dicyclomine, hyoscine, and valethamate are preferred anticholinergic drugs to relieve colic pain caused by various conditions like renal colic, abdominal colic, biliary colic, and dysmenorrhea.
- Usually antimuscarinic spasmolytics are combined with NSAIDs for the synergism in producing analgesia.

2.6.3 Management of Overactive Bladder

- Vasicoselective antimuscarinic drugs like tolterodine, fesoterodine, oxybutynin, darifenacin, trospium, and solifenacin are preferred to treat overactive bladder.
- Oxybutynin and trospium may cause dry mouth and other side effects due to non-selective antimuscarinic action. Other drugs specifically block M_3 receptors and side effects are expected to be less.

Table 2.4 Comparison of characteristic features of anticholinergic used in parkinsonism

Parameter	Trihexyphenidyl	Procyclidine	Biperiden	Orphenadrine
Oral bioavailability	100%	75%	87%	>95%
V_d (for 60 kg)	Unknown	60 L	24 L	Unknown
Protein binding	Unknown	Unknown	60%	95%
Metabolism	Not metabolized	Not metabolized	Hydroxylation	Liver
Active metabolite	Nil	Nil	Nil	Yes
Route of elimination	Renal and bile	Renal	Renal	Renal and bile
Half-life	32.7 h	11–12 h	18–24 h	13–20 h
Potency	High	Moderate	High	Low
Dose	1–3 mg TDS	2.5–5 mg TDS	2–4 mg TDS	50–100 mg BD
Strength/ formulation	2 mg tablet	2.5, 5 mg tablet	2 mg tablet	50 mg tablet
Common ADR	Dry mouth Tachycardia Blurred vision Confusion	Same like benzhexol	Orthostatic hypotension Bradycardia Blurred vision	Same like benzhexol

2.6.4 As Pre-Anesthetic Medication

- Glycopyrrolate, hyoscine, and atropine are commonly employed before anesthetic drug administration to reduce the salivary and tracheobronchial secretions.
- Glycopyrrolate and hyoscine are preferred over atropine. Glycopyrrolate has poor CNS action and does not cause delirium like atropine. Hyoscine has CNS depressant action with hypnotic action and aids in decreasing the anxiety in patients before surgery.

2.6.5 Bronchial Asthma and COPD

- Respiratory anticholinergics like ipratropium, tiotropium, aclidinium, and umeclidinium are preferred to cause bronchodilation in asthma and COPD.
- The efficacy of respiratory antimuscarinic is superior to beta adrenergic agonists in COPD patients (due to high vagal tone in COPD lungs). In case of asthma, respiratory antimuscarinic agents are less efficacious than beta adrenergic agonists. Respiratory antimuscarinic drugs improve the exercise capacity in COPD patients.
- Except ipratropium, other drugs have long duration of action and are commonly employed in prophylactic therapy. Beta adrenergic agonists are the drugs of choice to produce immediate symptomatic relief even in COPD.

Table 2.5 Comparison of characteristic features of anticholinergic used as vasicoselectives

Parameter	Oxybutynin	Tolterodine	Fesoterodine	Trospium	Darifenacin	Solifenacin
Receptor selectivity	M_1 and M_3	M_3	M_3	M_1 and M_3	M_3	M_3
Oral bioavailability	6–10%	77%	52%	9.6%	15–19%	90%
V_d (for 60 kg)	193 L	110–135 L	169 L	250–550 L	163 L	600 L
Protein binding	91–93%	96%	50%	50–85%	98%	98%
Metabolism	Liver (CYP3A4)	Liver CYP2D6 and CYP3A4	Prodrug metabolized to 5-OH methyl tolterodine	Ester hydrolysis by kidney	Hepatic CYP2D6 and CYP3A4	Hepatic CYP3A4
Active metabolite	Yes (*N*-desethyl oxybutynin)	Yes (5-OH methyl tolterodine)	No	No	No	Yes (4-OH solifenacin)
Route of elimination	Hepatic	Renal (75%) Feces (>15%)	Renal (90%) Hepatic (<10%)	Feces (85%) Renal (<5%)	Hepatic	Hepatic
Half-life	12–13 h	2–4 h	7–8 h	20 h	13–19 h	45–65 h
Potency	Moderate	High	High	Low	High	High
Dose	5–10 mg BD	1–2 mg BD	4–8 mg OD	20 mg BD	7.5–15 mg OD	5–10 mg OD
Strength/formulation	2.5 and 5 mg tablets	1, 2, and 4 mg tablets	4 and 8 mg tablets	10 and 20 mg tablets	7.5 and 15 mg tablets	5 and 10 mg tablets
Common (bolded) and other ADR	Dizziness Somnolence Xerostomia Constipation	Abdominal pain Constipation Xerostomia	Xerostomia Peripheral edema Skin rashes	Xerostomia Headache	Xerostomia Constipation Headache Blurred vision	Same as darifenacin

Table 2.6 Comparison of characteristic features of anticholinergic used as spasmolytics

Parameter	Hyoscine	Glycopyrrolate	Dicyclomine
Oral bioavailability	10–50%	<2%	65–67%
V_d (for 60 kg)	72–75 L	24–36 L	210 L
Protein binding	30–40%	Unknown	>99%
Metabolism	Liver (CYP3A4)	Liver CYP3A4 (minimal metabolism)	Not determined (liver)
Active metabolite	No	No	?
Route of elimination	Renal	Excreted unchanged renal (85%) Bile (<5%)	Renal (75%) Feces (<8%)
Half-life	4.5 h	0.6–1.2 h	2–10 h
Potency	Low	High	Moderate
Dose	20 mg QID	4 μg/kg	10–20 mg QID
Strength/formulation	20 mg/ml ampoule 10 mg tablet	0.2 mg/ml ampoule	10 mg/2 ml ampoule 10 mg tablet
Common (bolded) and other ADRs	Hypotension Xerostomia Constipation Tachycardia Blurred vision	Xerostomia Constipation Hypotension Dysuria	Dizziness Blurred vision Somnolence Dry mouth

2.6.6 Motion Sickness

- Hyoscine successfully blocks the cholinergic transmission from the vestibular apparatus to vomiting center. With additional CNS depressant action, hyoscine is preferred for motion sickness.
- Hyoscine is available as transdermal patch. It should be applied behind ear pinna before 3–4 h of journey. Hyoscine acts as a prophylactic drug and it is not effective when applied after development of vomiting during the journey.
- Because of hyoscine-induced sedation, the patient should be advised to avoid driving.

2.6.7 Arrhythmias

- Atropine shortens the AV nodal delay. Hence, atropine can be used to treat partial AV nodal block and sick sinus syndrome.

2.6.8 Drug-Induced Parkinsonism

- Anti-psychotics and other dopamine antagonists produce drug-induced parkinsonism. Centrally acting antimuscarinic drugs like benzhexol, biperiden,

procyclidine, and orphenadrine are used to counteract the increased muscarinic activity in the striatum.
- Central anticholinergics are efficacious only in drug-induced Parkinsonism. In case of primary and idiopathic Parkinsonism, central anticholinergics are less efficacious than dopamine agonists or L-DOPA.
- Tremors in parkinsonism are reduced better than the rigidity by anticholinergic drugs.

2.6.9 In Poisoning

- Atropine is the drug of choice and antidote for counteracting the muscarinic effects in organophosphorus, carbamate, and nerve gas poisoning. Atropine reverses all the overactive muscarinic symptoms like bradycardia, miosis, sweating, increased glandular secretion, and diarrhea within minutes of administration.
- Atropine is also the antidote of choice for "early mushroom poisoning" caused by *Amanita muscaria*.
- In snake poisoning, along with neostigmine, atropine is given to counteract bradycardia and bronchospasm by neostigmine.

2.6.10 Other Uses with Unproven Efficacy

- Propantheline, pirenzepine, and telenzepine were used to reduce the acid secretion in peptic ulcer. These drugs are of low efficacy and are superseded currently by PPIs and H_2 blockers.
- Anticholinergics are tried to reduce the bronchial secretion that occurs reflexively in pulmonary embolism. The efficacy of antimuscarinic is doubtful in this setting and warrants extreme caution.

2.7 Adverse Effects and Contraindications

- The major adverse effects noted in anticholinergic therapy are due to blockade of muscarinic receptors in unintended organs.
  - Tachycardia
  - Xerostomia
  - Urinary retention
  - Delirium, hallucination
  - Hyperthermia
  - Blurred vision
- Antimuscarinic drugs are contraindicated in patients with narrow corneal angle (precipitates glaucoma), benign prostate hypertrophy (urinary retention is aggravated), hyperthyroidism (aggravates palpitations), coronary artery disease

(aggravates workload of heart by producing tachycardia), and arrhythmia (precipitates tachyarrhythmias).

2.8 Management of Anticholinergic Poisoning

- Commonly seen when high dose of antimuscarinic drugs is used in adults, normal dose in children, and poisoning with suicidal or homicidal intentions.
- Classical symptoms occurring in anticholinergic poisoning ("anticholinergic toxidrome") are explained with the following mnemonic:
  - *Red as a beet* → cutaneous vasodilation
  - *Mad as a hatter* → delirium by CNS excitation
  - *Blind as a bat* → Mydriasis leading to loss of accommodation
  - *Hot as a hare* → Hyperthermia due to loss of sweat and hypothalamic stimulation
  - *Dry as a bone* → Dryness due to loss of secretions from glands
- Management is symptomatic with monitoring of vitals. Gastric lavage with $KMnO_4$ should be done, if route of poison is oral. Cold sponging should be done to reduce hyperthermia. Diazepam can be used to prevent seizures.
- Physostigmine or neostigmine can be used with caution to counteract the symptoms. However, in clinical setting this is seldom practiced.

2.9 Ganglion Blockers

- Drugs: Hexamethonium, pentolinium, mecamylamine, pempidine, high dose nicotine, and trimethaphan.
- The actions produced by ganglion blockers depend upon the "dominant system" of ANS involved in the particular organ.
  - Tachycardia in heart (blockade of parasympathetic ganglion).
  - Vasodilatation in blood vessel (blockade of sympathetic ganglion).
  - Loss of sweating (blockade of sympathetic tone).
  - Mydriasis and cycloplegia in eyes (blockade of ciliary ganglion).
  - Loss of erection and difficulty in micturition (blockade of sacral parasympathetic outflow).
  - Loss of ejaculation (blockade of sympathetic tone).
- Many of these drugs were used to treat hypertension and currently are obsolete. At present ganglionic blockers are of only toxicological interest with no clinical use.

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