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„Antipasmodic drugs acting on smooth and
skeletal muscles “

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List of abbreviations:

C.N.S: Central nervous system.

I.B.S: irritable bowel syndrome.

G.I.T: gastrointestinal system.

O.A.B: overactive bladder .

I.C.U: intensive care unit.

C.V: cardiovascular.

C.V.S: cardiovascular system.

M.O.A: mode of action.

C.I: contraindications.

S.E: side effects.

Introduction

A muscle spasm is an involuntary contraction of the affected muscle that can occur in any muscle of the body due to abnormal nerve stimulation or abnormal activity of the muscle itself. These spasms can attack skeletal muscles as in case of neurological disorders that represent the most serious form of spasm and in this case the muscle spasm is called spasticity. However the most common form of spasm involves the smooth muscle especially the gastrointestinal tract. So use the drug in the treatment of such spasm is known as spasmolytic or antispasmodic drug.

Depending on which muscles involved and the cause of the spasm, antispasmodic drugs can be classified into:

(A) Drugs used in the therapy of visceral smooth muscle spasms are substances that relax smooth muscles and can be classified into:

1- Specific antimuscarinic activity (atropine-like drugs):

Antimuscarinic drugs act as competitive inhibitor on muscarinic receptors at smooth muscles. Can be classified in the following manner (Vardanyan and Hurby, 2006):

- **Alkaloids** as atropine, scopolamine and hyoscyamine, are the most important. They are used in the treatment of pylorospasm, peptic ulcer, renal colics, cholecystitis and bronchial asthma.
- **Anticholinergic of quaternary amine:** synthetic substances with more spasmolytic and less anticholinergic action with a fewer side effects and used in treatment of pylorospasm, hyperperistalsis and stomach ulcer. The list of these drugs include:
 - Anisotropin, clindinium, glycopyrrolate, hexacyclium, isopropamide, mepenzolat, methanteline, meth-scopolamine, propantheline,
- **Antiparkinsonism of tertiary amines:** as dicyclomine, oxybutynin and oxyphencyclimine. They are effective in treatment of irritable bowel syndrome and urinary incontinence.
- **Mydriatics of the tertiary amine series:** as cyclopentolate and tropicamide. They are used in ophthalmological examination (Vardanyan and Hurby, 2006)

Some anticholinergic drugs act more specifically in genitourinary system, to treat patients with urinary incontinence as Darifenacin, emepronium , fesoterodine, flavoxate, imidafenacin, meladrazine, mirabegron, oxybutynin, propiverine, solifenacin, terodiline, tolterodine and trospium chloride (Canney, 2006)

2- Non-specific activity (papaverine-like direct spasmolytics):

Papaverine is opium alkaloid used in the treatment of spasms of the gastrointestinal tract, bile ducts and ureter. It may also be used as a smooth muscle relaxant in microsurgery where it is applied directly to blood vessels (Milovanovic , 1997)

Mebeverine: is a musculotropic antispasmodic, derivative of reserpine. It has a selective action on IBS with fewer side effects than other anticholinergics (Seth, 2009).

3-Herbal therapy:

Peppermint, chamomile, fennel, celery seed and calamus: are used primarily in the treatment of abdominal colics caused by menstrual cramps or cramps of peristaltic movements. They have properties in treating mild digestive system disturbances and related complains (Tyler, 1999).

4-Organic nitrates: relax smooth muscles efficiently, but this effect is short lasting due to their rapid liver metabolism (Milovanovic et al, 1997)

Other drugs as calcium channel blockers have a minor role as spasmolytics and have no specific action in the treatment of IBS (Dickhaus, 2002).

(A) Drugs that affect skeletal muscle function categorized into two major groups according to their therapeutic action:

(1) Drugs used to decrease spasticity (acting mainly on central nervous system)

Spasticity present in different neurological diseases as in cerebral palsy, multiple sclerosis, spinal cord disease and stroke. In these diseases there is a hypertonia together with muscle weakness. The underlying mechanisms of this spasticity appear to involve not the stretch arc itself but due to injury in higher brain centres with damage to descending pathways which in turn leading to hyperactive stretch arc. Using spasmolytic drugs may reduce symptoms of spasticity by modifying the stretch reflex arc or by interfering skeletal muscle contraction. While several available drugs can cause significant relief from painful muscle spasm, they are less effective in the recovery of muscle function in these patients. Examples of these drugs include:

- **Benzodiazepines as diazepam:** is γ -aminobutyric acid (GABA) agonist in the central nervous system. The site of action mainly in spinal cord because it is found that this drug is effective in patients with spinal cord transaction however, it can be used with muscle spasm of any origin including local muscle trauma. Other benzodiazepines have been used as spasmolytics, but experience with them is much more limited.
- **Baclofen:** is an orally active GABA-mimetic agent. Stimulation of GABA receptors in the brain by baclofen results in hyperpolarization and subsequent decrease the release of excitatory neurotransmitters in the CNS. Baclofen has a role in reducing the pain accompanied with spasticity may be by inhibition of substance P release in the spinal cord. Using of this drug with precaution in epileptic patients as it may lead to provocation of seizure. Intrathecal administration is very useful in control severe spasticity and pain that is not responsive to other medication, after several month of therapy tolerance may occur which can be overcome by appropriate dosage adjustment to maintain the significant effect of the drug.
- **Tizanidine:** is α_2 -adrenoreceptor agonist. It has a significant effect in patient with spasticity nearly as same as the effect of diazepam, baclofen and dantrolene, but it has more side effects as hypotension, drowsiness and dry mouth.
- **Other drugs that act in the CNS:** Gabapentin, progabide, glycine, idrocilamide and riluzole.

- **Dantrolen:** is a hydantion derivative. Its spasmodic action outside central nervous system as it reduces skeletal muscle strength by interfering with excitation contraction coupling at the level of skeletal muscle fiber. It has a little depressant effect on cardiac and smooth muscles.
- **Botulinum Toxin:** local injection of botulinum toxin is not only used for local muscle spasm but also in generalized spastic disorder. The effect of a single injection in one or two limbs may persist for several months.
- **Drugs used for acute local muscle spasm:** These drugs can be used in case of acute temporary muscle spasm caused by local trauma or strain. They act as sedatives at the level of spinal cord or brain stem. Examples for these drugs are: carisoprodol, chlorphenesin, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol and orphenadrine (Miller, 2001)

(2) Neuromuscular blocking drugs are used as adjuvant to general anaesthesia to interfere with transmission at neuromuscular end plate but do not act on CNS. Mode of action of these drugs through one of two pathways:

(a) Non-depolarizing blocking drugs: these drugs antagonize the action of acetylcholine on nicotinic receptors and thus prevent depolarization. These drugs include

- **Isoquinoline derivatives:** They have long duration of action as atracurium, cisatracurium, doxacurium, metocurine and tubocurarine. The shortest duration of action of them is mivacurium.
- **Steroid derivatives:** they have weak action as pancuronium, pipecuronium, rocuronium, and vecuronium.

(b) Depolarizing drugs: blocking of nicotinic receptor by an excess of depolarizing agonist. The only depolarizing agent used clinically in the USA is succinylcholine. Its action is similar to that of acetylcholine but with a longer effect (Miller 2001).

Aim of work

The aim of this work is to review the literature to study the effectiveness of antispasmodic drugs in the treatment of smooth and skeletal muscle spasms.

CHAPTER(1)

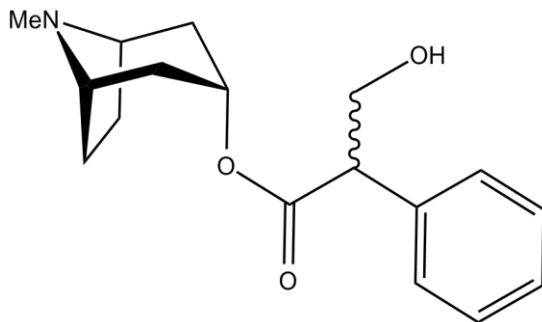
Effect of antispasmodic drugs on smooth muscles

- **Specific antimuscarinic activity (atropine – like drugs):**

Belladonna Alkaloids as atropine, scopolamine and hyoscyamine:

- * **Atropine:** Obtained from the plants of *Atropa belladonna* (Pretty lady) [*Datura – stramonium*]. It doesn't completely abolish the effects of vagal stimulation. In large doses, it can also block nicotinic receptors of Acetylcholine at the autonomic ganglia.

Pharmacological action of Atropine and scopolamine are similar except atropine is C.N.S. (central – nervous system) stimulant while scopolamine is C.N.S. depressant. Atropine is more selective on heart, gut, bronchial smooth muscle and has a longer duration than scopolamine.



Fig(1): structure of atropine.

Action on smooth muscle:

1. **Gastrointestinal – Tract (GTT):** It decreases tone and motility of gut. It antagonizes spasmogenic action of morphine on intestine and can abolish the excessive motility induced by cholinergic agents so it is used in treatment of Gastric colic.

It reduces the secretions of many organs such as stomach acid production, secretion from the pancreas, decrease secretions of the nose, lungs, salivary glands and stomach before surgery.

2. **Biliary Tract:** It exerts a weak – relaxant action on the biliary tract and the gall – bladder.
3. **Urinary – Tract:** It reduces the tone of the bladder and enhance the tone of the sphincter and can cause urinary- retention so, it is contraindicated in benign–prostatic- Hyperplasia.

Atropine, Morphine combination used to relieve renal colic. It acts probably by increasing capacity of bladder as a result of its relaxant effect on bladder wall. So, it is used to treat the urgency and frequency of micturition in patients with paraplegia.

4. **Bronchi:** It relaxes the smooth muscles of the bronchi. It is effective in relieving broncho-constriction produced by cholinergic agents but is less potent than adrenaline in relieving histamine induced broncho- constriction. It dry-up mucus production associated with infections, diseases and allergies. So, it is used as a pre anesthetic medication to reduce respiratory secretions.

5. **Uterus:**

Atropine and scopolamine have no effect on uterine smooth muscle.

6. **Eye:**

Produces mydriasis by blocking the cholinergic nerve supplying the smooth muscle of the sphincter of the iris. Atropine is thus both a mydriatic and a cycloplegic drug.

7. **Cardiovascular system (C.V.S):**

Reduces heart rate, it abolishes the effects of cholinergic agents on the heart rate. It counters the vaso-dilation and hypotension produced by cholinergic agents. Toxic doses produce dilatation of the Blood vessels resulting in atropine flush and hypotension. It abolishes A.V. Block due to excessive vagal activity.

8. **Central- nervous – system (C.N.S):**

It causes a stimulation of medullary vagal nuclei and higher cerebral centres. This produces bradycardia and increase in the rate and depth of respiration. Respiratory depression produced by toxic doses of anticholinesterases can be antagonized by atropine administration. Atropine in moderate doses, controls the tremors and rigidity in parkinsonism. In toxic doses, it produces excitation. In contrast to atropine, scopolamine depress

the reticular activating system and produce euphoria, drowsiness and dreamless sleep.

*** Pharmacokinetics:**

Belladonna alkaloids are absorbed from G.I.T (Gastrointestinal tract) Atropine is partly detoxified in liver and partly excreted unchanged by kidneys. It has plasma $t_{1/2}$ of 4 hours. It crosses placental barrier and is secreted in milk and saliva.

*** Side – effects:**

Dryness of mouth, difficulty in swallowing. Tachycardia, fever, constipation, blurring of vision. It can precipitate glaucoma especially in the elderly. It is contraindicated in enlarged prostate as retention of urine. (Satoskar 2009).

*** Synthetic and semi-synthetic Atropine substitutes:**

Produce more therapeutic selectivity than atropine. These atropine substitutes are:

1. Quaternary – ammonium – compounds.
2. Tertiary – amine – drugs.

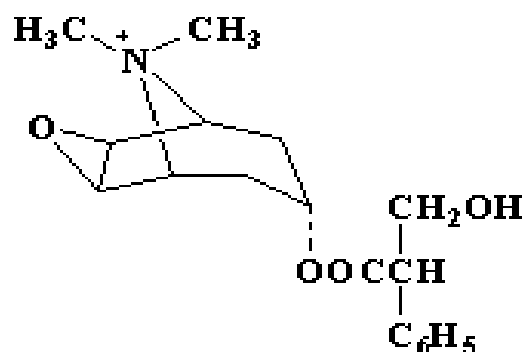
*** Atropine substitutes as Antiparkinsonism drugs of Quaternary – ammonium – compounds:**

Are not orally absorbed, do not cross the blood – brain – barrier and exhibit a great degree of nicotinic (ganglionic) blocking action. They act centrally in treating parkinsonism by reducing rigidity but they have little effect on tremors.

*** Methscopolamine:**

Is devoid of central effects of scopolamine and is used in treatment of renal – colic and frequency of micturition associated with cystitis.

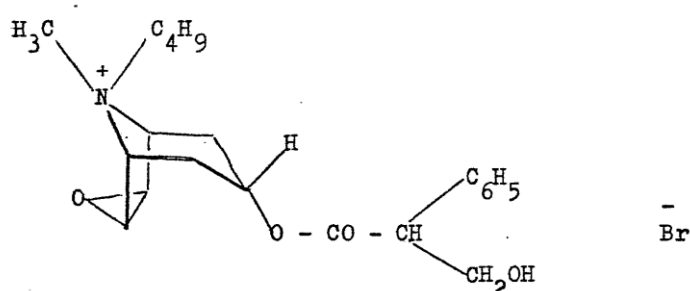
Methscopolamine
 $C_{18}H_{24}NO_4$



Figure(2): structure of methscopolamine.

*** Methantheline (Banthine):**

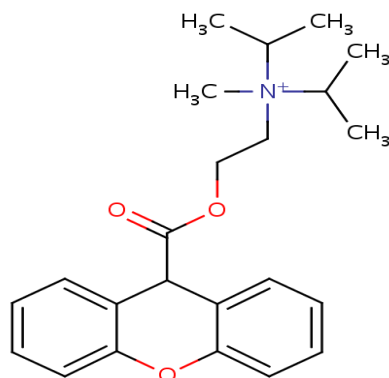
Is a synthetic quaternary ammonium compound with a high ratio of ganglion blocking to muscarinic blocking activity. The Gastrointestinal effects and the duration of action of this drug are greater than those of atropine. The drug may produce impotence, postural hypotension, urinary retention and neuromuscular – blockade.



Figure(3):structure of methantheline

*** Propantheline:**

It is related to methantheline and possess more potent ganglionic and muscarinic blocking actions than methantheline. It has been used as a muscle relaxant in irritable – bowel – syndrome (I.B.S)

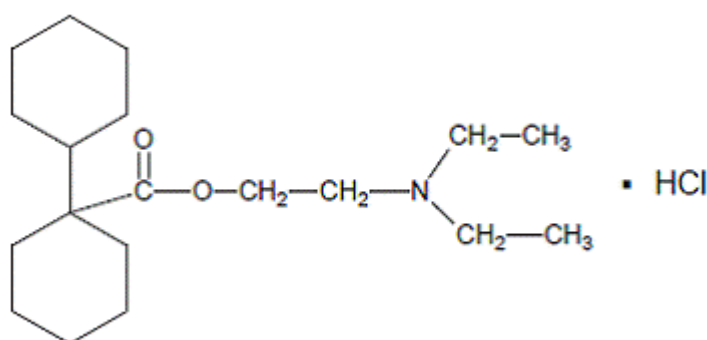


Figure(4):structure of propantheline.

2. Tertiaryamines as:

- Dicycolmine:

It has direct relaxant properties. It is used in dysmenorrhoea, irritable – bowel – syndrome and urinary incontinence.

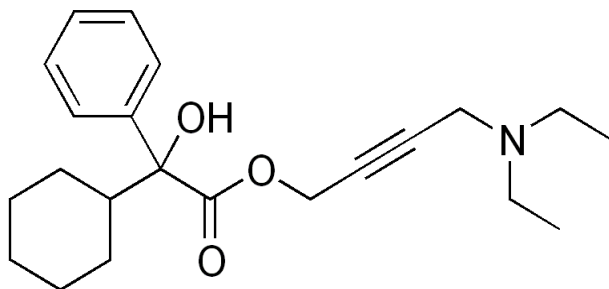


Figure(5):structure of dicycolamine

- Oxybutyin (Ditropan, Tropan):

It has anaesthetic effects on the urinary bladder. It has been used in treatment of urinary urgency, urinary incontinence and urinary frequency expect that following transurethral surgical procedure. It decrease gastrointestinal

motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony colitis . (Satoskar 2009)



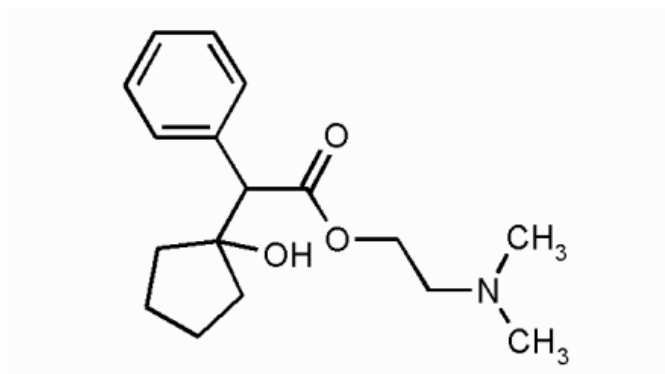
Figure(6):structure of oxybutynin

- **Mydriatics of the tertiary amine series:**

- 1-cyclopentolate:**

It is the preferred choice for cycloplegia over atropine and homatropine. Ophthalmic solution is in the form of cyclopentolate hydrochloride, a white crystalline powder. Cyclopentolate works faster and the duration of action is shorter than atropine and homatropine.

Side effects:are rare but can include effects such as disorientation, incoherent speech or visual disturbances during the 24-hour period that the drug has an effect. The side effects are more common in children.

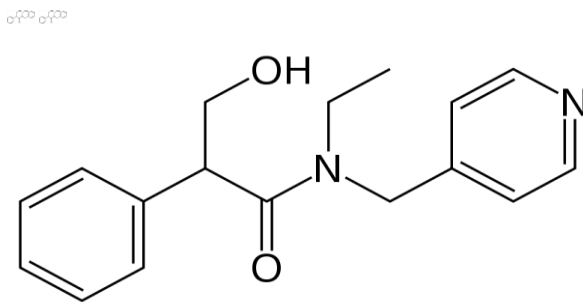


Figure(7): structure of cyclopentolate

2-Tropicamide: It is a synthetic derivative of tropic acid. Its lipid solubility allows a greater penetration through the cornea and therefore a more rapid effect and shorter duration of action than cyclopentolate. It is available in 5% and 1% concentrations. Cycloplegia occurs in 10-15 minutes and lasts up to 6 hours. However, its efficacy is lower than cyclopentolate.

Side effects: It may cause redness or inflammation and also blurs near vision for a short while after instillation. It may, in very rare cases cause an attack of acute angle closure glaucoma.

It is often preferred to atropine because atropine has a longer half-life, causing a prolonged dilation and blurry vision for up to a week. Systemic side effects are very rare.(Lam 2009)



Figure(8): structure of tropicamide.

- **Anticholinergic drugs:**

- 1) **Darifenacin: (Enablex):**

It is a bladder antispasmodic; it is indicated for treatment of overactive bladder with symptoms of urge incontinence, including urgency and frequency. It antagonizes the effect of Acetylcholine on muscarinic receptors in detrusor muscle, decreasing muscle spasms that cause inappropriate bladder emptying. This action increases bladder capacity and volume which relieves sensations of urgency and frequency and enhances bladder control.

Contraindications:

Gastric retention, hypersensitivity to darifenacin or its components,

Uncontrolled narrow-angle glaucoma, urine retention and patients at risk for these conditions. Interactions with drugs as Anticholinergics causes increased frequency and severity of Anticholinergic adverse reactions

Adverse reactions:

CNS: Asthenia, confusion, dizziness, hallucinations.

CV: Hypertension, peripheral edema

EENT: Abnormal vision, dry eyes or mouth, pharyngitis, rhinitis, sinusitis.

GI: Abdominal pain, constipation, diarrhea, indigestion, nausea, vomiting.

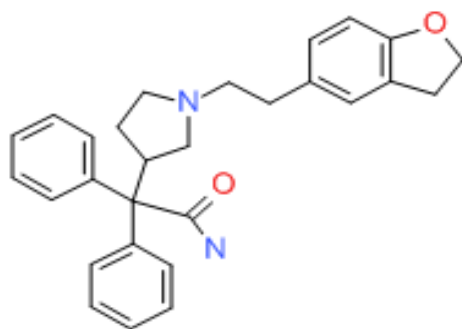
GU: urine retention, UTI, vaginitis

MS: Arthralgia, back-pain.

RESP: Bronchitis.

Skin: dry skin, pruritis, rash

Other: Angioedema, flu-like symptoms, hypersensitivity reactions, weight gain (Jones and Bartlett Publishers 2010).



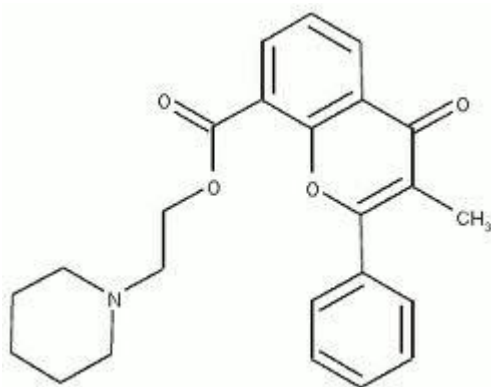
Figure(9):structure of Darifenacin

2) **Flavoxate:**

The main mechanism of the effect of flavoxate on smooth muscle has not been established. It has moderate Calcium antagonistic activity, inhibits phosphodiesterase, and has local anaesthetic properties. No

anticholinergic effect has been found. The clinical effects of flavoxate in patients with detrusor instability and frequency, urge and incontinence have been studied in both open and controlled investigations with varying rates of success.

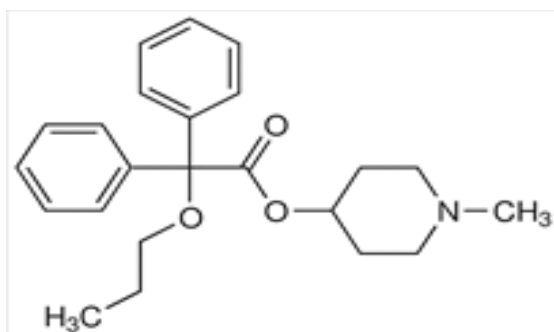
It has few and mild side-effects, but its efficacy compared to other therapeutic alternatives is not well documented (Katz 2004).



Figure(10):Structure of flavoxate

3) **Propiverine:**

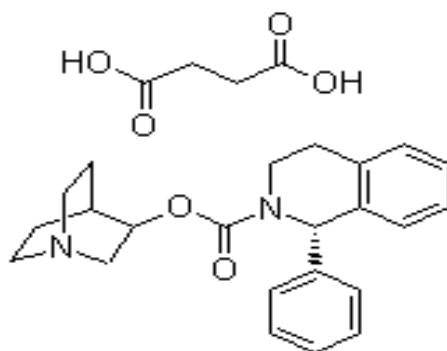
It has combined anticholinergic and calcium antagonistic actions. It's rapidly absorbed but has a high first pass metabolism. It has been shown in several investigations to have beneficial effects in patients with detrusor over activity (Andersson 2003).



Figure(11): structure of propiverine.

4) **Solifenacin**:

It is an M3 muscarinic receptor antagonist for treatment of overactive bladder in Europe. It is contraindicated in patients with hepatic impairment, gastric retention, urinary retention or uncontrolled narrow angle glaucoma (Hedge 2005).

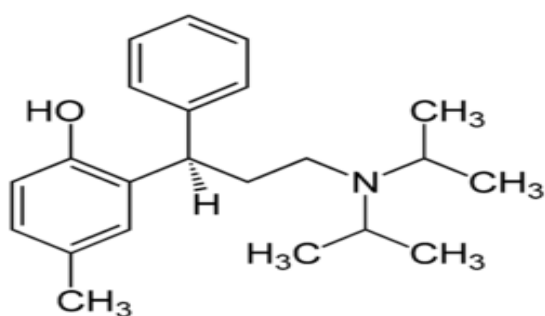


Figure(12):Structure of solifenacin

5) **Tolterodine**:

It is used to treat overactive bladder, to help manage the symptoms of urinary frequency, urgency, and urge incontinence. It is a highly protein-bound drug, although its active metabolites is not. First pass metabolism occurs after an oral dose. Excretion of drug and metabolites is in the urine, primarily and in the stool. It is a competitive cholinergic muscarinic antagonist. It is contra-indicated if the patient has urinary retention, gastric retention, uncontrolled narrow angle glaucoma or hypersensitivity to the drug.

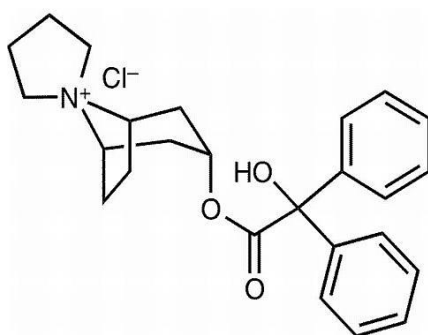
Side effects: are dry mouth, headaches, constipation, abnormal vision, urinary retention and xerophthalmia (Aschenbrenner 2009).



Figure(13):structure of tolterodine

6) **Trospiumchloride:**

Is an antimuscarinic that has been used in Europe for management of OAB symptoms. It's chemical structure is such that it is unlikely to penetrate the brain and thus does not appear to affect cognitive function. It is not well-absorbed if taken with food. It's advantage is that it has little potential interaction with other medications. Trospiumchloride extended release is excreted intact by the kidney with essentially more of the drug metabolized by the liver (Ellsworth 2010).

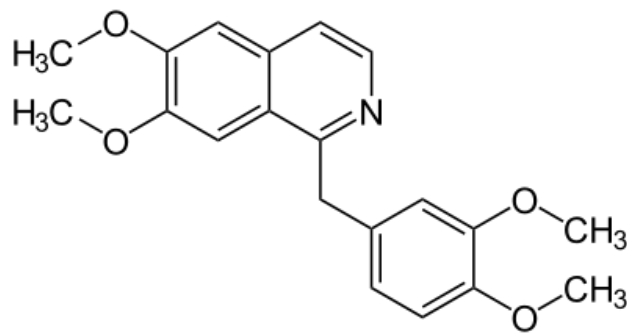


Figure(14):Structure of trospium chloride

- **Non-specific activity (Papaverine-like Spasmolytics):**

- 1) **Papaverine:**

Belongs to a class of drugs known as vasodilators which expand blood vessels, therefore increases blood flow and is generally used to treat poor blood circulation. Self-injection of Papaverine into the penis combined with small doses of phentolamine mesylate has been effective for erectile dysfunction, increasing swelling of the penis and resulting in an erection. Papaverine injection is one of the most effective well-studied drugs for erectile disorders. (Lowghlin 2006).



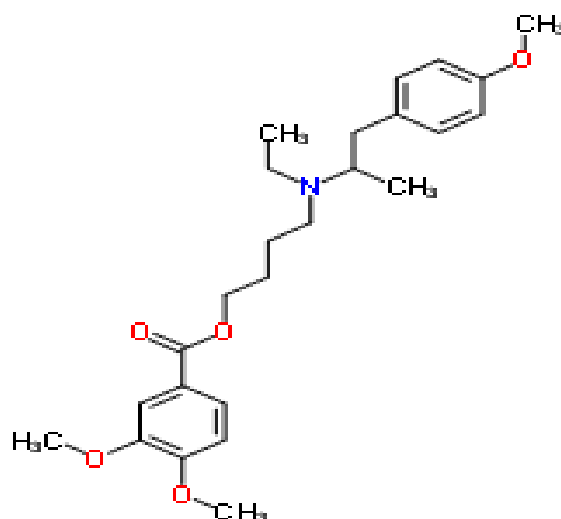
Figure(15):structure of papaverine

- 2) **Mebeverine:**

It is a derivative of reserpine. It is a musculotropic antispasmodic which acts directly at the cellular level. In the gut it has 2 components: first, it exerts an antispasmodic effect by reducing the membrane permeability of smooth muscle cells.

Second, it indirectly reduces K⁺ ion efflux, thus avoiding hypotonia. Anticholinergic effects are less as it does not act by autonomic nervous system. It is rapidly and completely absorbed after oral administration. It is not excreted as such, but is metabolized completely. It is 75% protein bound. It is indicated in IBS in its primary form or associated with organic lesions of GIT and smooth muscle

spasm. Paralytic ileus is a contraindication. Unwanted effects are fever and include heart burn, dizziness, indigestion, headache and constipation. It is contraindicated in children less than two years of age and in patients with hypersensitivity to it. During pregnancy and lactation, it should be used cautiously. (Saraya 2009)



Figure(16):Structure of mebeverine

Herbal Therapy:

1) Peppermint Oil:

It is obtained by steam distillation from the fresh overground parts of the flowering plant of *Mentha*.

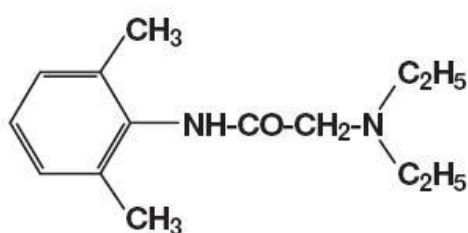
The main constituents of the oil are menthol with smaller amounts of menthol, isomenthol and menthone.

It is used internally for treatment of IBS, flatulence, coughs and cold and externally for rheumatic complaints, tension-type headache, pruritis, urticaria and pain in irritable skin conditions

. It is administrated orally, locally or inhalation. It is contraindicated with contact sensitivity to it and it should be used only in enteric-coated capsules with medication with H₂-receptor blockers to prevent interaction and it should not be used during pregnancy or lactation without medical advice.

Persons suffering from reflex oesophagitis are affected by heart-burn from it.

Undesirable effects such as nausea, anorexia, cardiac problems, ataxia and other CNS problems are caused due to excessive inhalation of mentholated products containing volatile menthol (ESCOP Monographs 2003).



Figure(17):structure of peppermint oil.

2) **Chamomile:**

It has been used as Medicines since traditionally grouped in botanical texts.

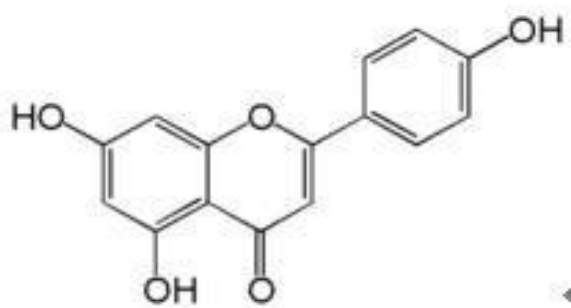
It was used in jaundice, fevers, Kidney stones, colic, retention of urine and inflammation of the bowel, treatment colic in infants, teething pains and fever. Chammoile tea is very popular and its extracts are also used in cosmetics as bath preparations, in hair dye for blonde hair, shampoo, mouth-washes and preparation to prevent sun-burn. It consists of Essential-oil, Flavonoids, coumarins, proazulenes and plant acids. Chammoile extract (Essential oil) produced by a cold-extraction process and steam distillation-process. It has anti-inflammatory action, antipuritic, antispasmodic, sedative, antimicrobial and antiuccler.

It is used in skin conditions such as in wound healing, Eczema and Dermatitis.

It is used in Gastric conditions such as Diarrhea, and in Anti-bacterial preparations.

Other uses for chamomile are oral mucositis, preventing sore-throat and haemorrhagic cystitis.

Adverse reactions: Allergic reactions and interactions with drugs such as with Benzodiazepines and warfarin. It is contraindicated in hypersensitivity to it (Brown 2007).



Figure(18):Structure of chamomile

3) **Fennel:**

It is widely activated throughout India. Parts used are seeds, oil, root.

It cures colic pain, vomiting, flatulence, burning syndrome, anorexia, used also as appetizer, carminative, spasmolytic and expectorant. It contains volatile oil, flavonoids, coumarins, tannis.

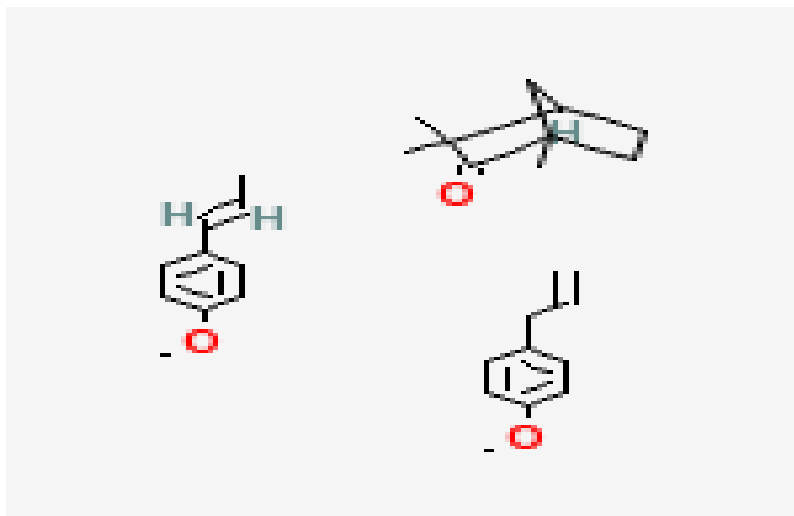
It exhibits gastrointestinal activity mobility and antispasmodic effect in higher concentrations.

It is used in dyspepsia, fullness, flatulence, for catarrh of upper respiratory tract in children.

It is mixed with strong laxatives for counteracting intestinal cramps.

The seeds are also used in losing weight.

It is CI during pregnancy (Kharee 2004)



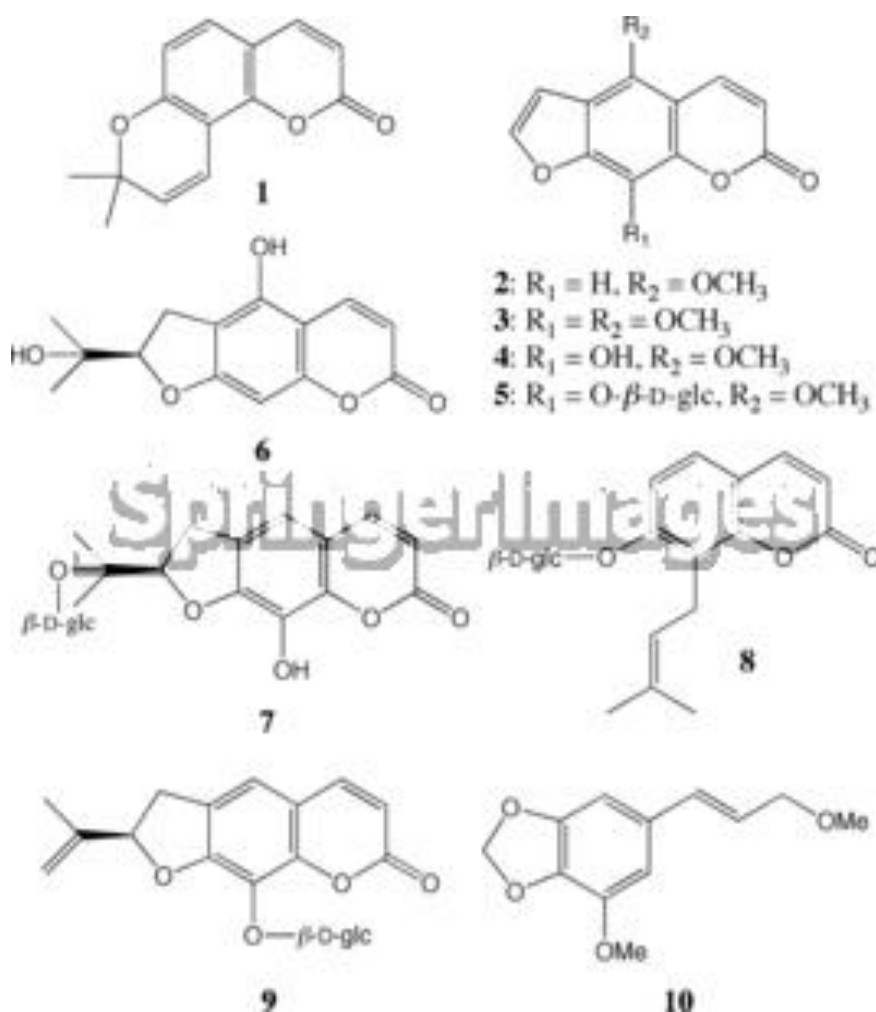
Figure(19):structure of fennel

4) **Celery-seed:**

Part used is ripe fruit (referred to as seed). It is used in arthritic disease, gout and urinary-tract inflammation, Antirheumatic, mild diuretic, mild spasmolytic and anti-inflammatory.

Its constituents are essential oil containing phthalides and furanocoumarins.

It is not used during lactation without medicinal advice, this is a C.I. Caution is advised in kidney disorders, esp. in inflammation of kidneys (Morgan 2005).



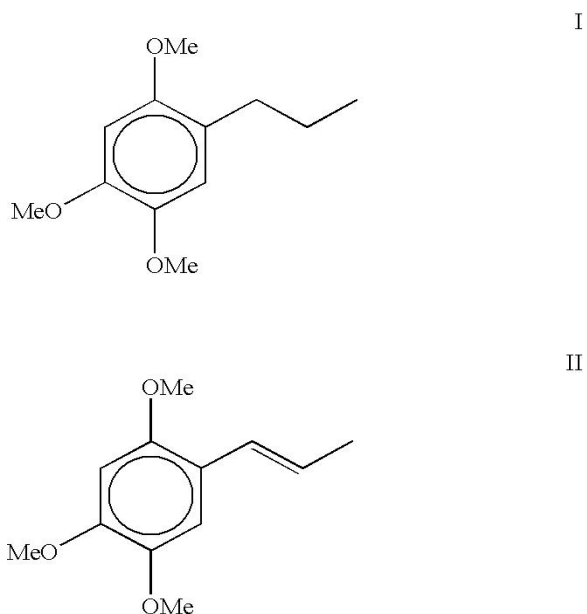
Figure(20): structure of celery seeds.

5)Calamus:

It is cultivated in India. Rhizome is the part used. It is used as purgative, appetizer, in haemorrhage, fever, urinary and skin diseases.

It is used internally in epilepsy, asthma, consumption, haemorrhage, impotence and also as a cardiac tonic.

Its constituents are calamenol, calamine and camphene. So, used as carminative, antispasmodic and antibacterial properties due to synergistic action of those active ingredients (Khare 2004)



Figure(21):Structure of calamus

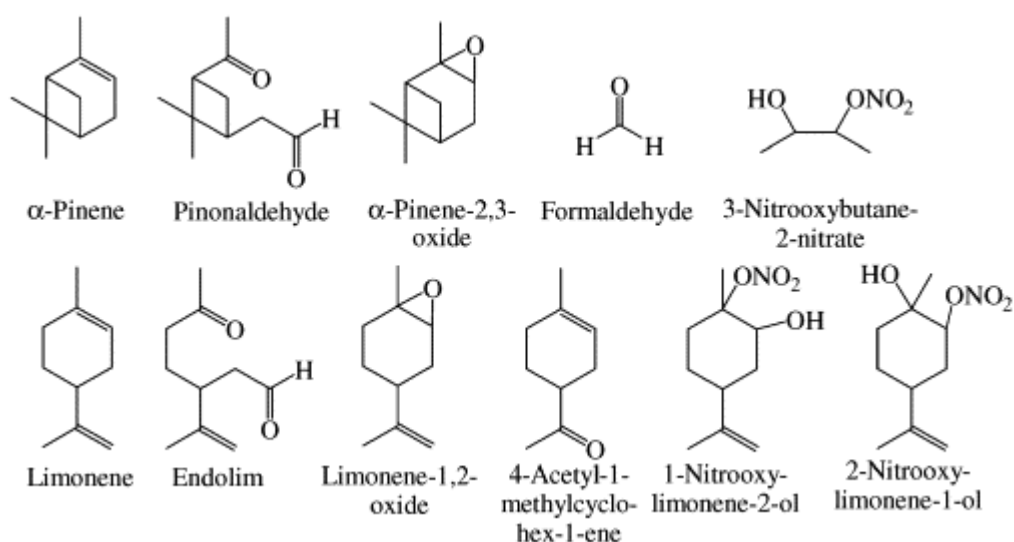
Nitrates:

They are used in treatment of Angina Pectoris, they are classified into rapid onset, short acting and slow onset, long acting. They are lipid – soluble – substance, thus absorbed from GIT.

They have a relaxant action on smooth muscles, dilate both arterioles and venules, as a spasmolytic in biliary colic.

Side effects: head ache, postural hypotension, glaucoma, tolerance and skin rash.

C.I.: acute myocardial infarction and severe anaemia. (Das. 2009)



Figure(22):structure of nitrates

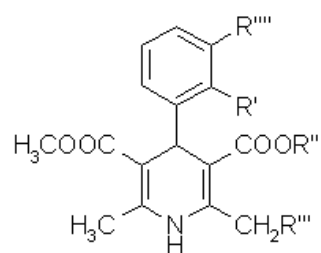
Calcium-channel-Blockers:

Verapamil and diltiazem.

They have been used in treatment of IBS through smooth muscle relaxant properties.

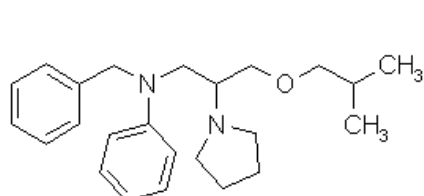
Peppermint oil decreases calcium influx which relaxes gastric intestinal smooth-muscle.

There are no controlled studies to support the use of Calcium-channel-blockers as a whole in treatment of irritable-bowel-syndrome (IBS). (Dickhous 2002).

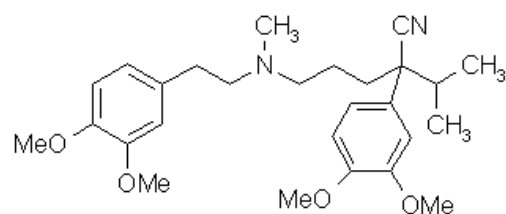


	R'	R''	R'''	R''''
Nifedipine	NO ₂	CH ₃	H	H
Amlodipine	Cl	CH ₂ CH ₃	O(CH ₂) ₂ NH ₂	H
Nicardipine	H	(CH ₂) ₂ N(CH ₃)CH ₂ C ₆ H ₅	H	NO ₂

1,4-Dihydropyridines

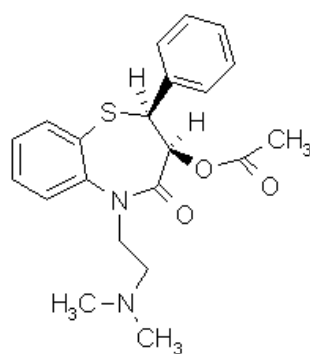


Bepridil



Verapamil

Phenylalkylamines



Diltiazem

Benzothiazepine

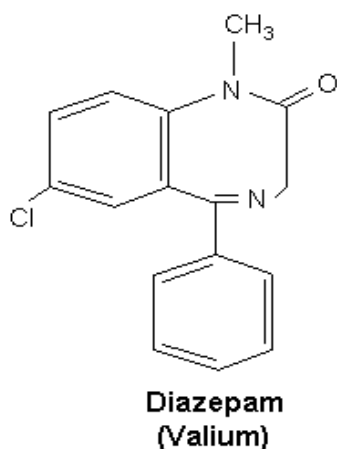
Figure(23):structure of calcium channel blockers

CHAPTER(2)

Effect of antispasmodic drugs on skeletal muscles

Diazepam:

It acts through the GABA system. It is metabolized in the liver, so it may cause side effects in individuals with liver dysfunction. Benzodiazepines may affect cognitive performance measures such as attention, concentration and memory and are not recommended in persons with brain injury. It produces depression of central – nervous- system, which can decrease the level of arousal , can cause sedation and impaired motor coordination, impair memory and attention, and may cause respiratory depression and coma in overdose. (Brashear 2011).



Figure(24):structure of diazepam

Baclofen:

Oral Baclofen was approved by the food and drug administration for spasticity and is currently the most effective and widely used drug for treatment of spinal – cord or cerebral spasticity.

It is slightly more lipid-soluble and crosses the blood – brain – barrier if given in high concentrations. Baclofen is not broken down by neural-

tissue. Oral Baclofen is shown to be an effective agent in spasticity caused by multiple sclerosis, spinal – cord – injury head trauma , and cerebral palsy.

Side effects of Baclofen:

Can be severe and include drowsiness and mental confusion. Other risks include seizures, psychic symptoms, and hyperthermia.(Hsieh 2009).

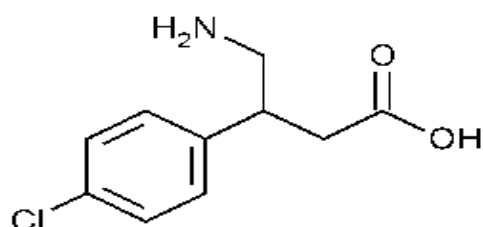
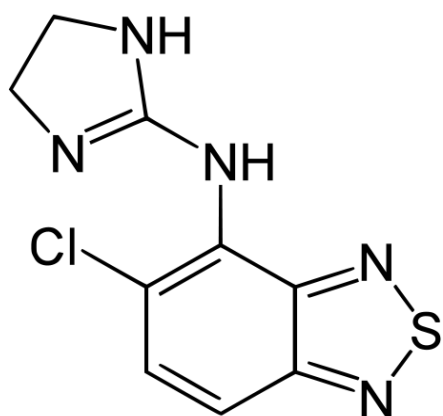


Figure (25):structure of baclofen

*** Tizanidine:**

Is centrally acting adrenergic α_2 receptor agonist used to treat chronic muscle spasticity conditions. It is the only antispastic skeletal muscle relaxant to treat low- back – pain. It is structurally related to α_2 – agonist- clonidine that is used to treat hypertension. Patients may experience hypotension with tizanidine, together with muscle weakness that may result in dizziness. It is rapidly and almost completely absorbed from the gastro – intestinal- tract, however, the estimated bioavailability is Only 10% to 15% because of extensive first pass metabolism.

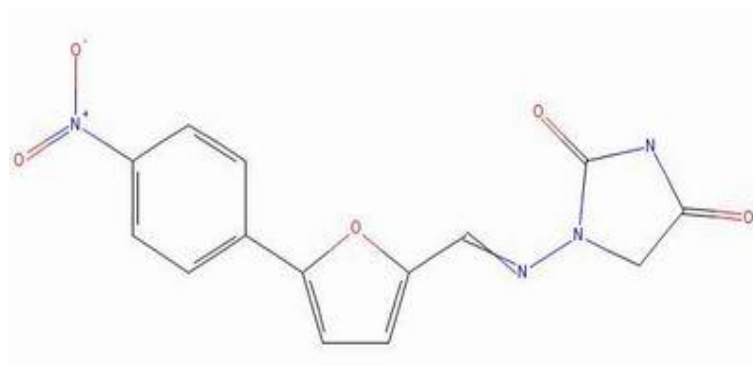
Side effects: are drowsiness and dry mouth. (Lemke 2011).



Figure(26):structure of tiazinidine

Dantrolene:

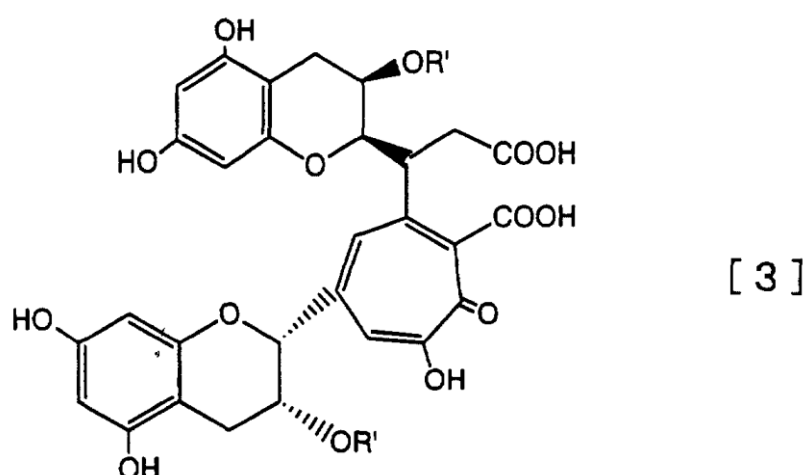
It is indicated for use in spinal cord injury, stroke, cerebral palsy and multiple sclerosis. Its site of action is to be at the sarcoplasmic reticulum in skeletal muscle – cells. It binds to a calcium channel protein on the sarcoplasmic reticulum to close the channel and inhibit the release of calcium. It is a weak base than can cross the blood brain barrier, thus central nervous system depressant side effects (e.g. sedation) are common. It is slowly metabolized by the liver to give metabolites and uncharged drug excreted in the urine for treating malignant hyperthermia it is administered intravenously. (Lemke 2011).



Figure(27):structure of dantrolene

Botulinium toxin:

Are neurotoxins produced by *Clostridium botulinum* that block acetylcholine release at the neuromuscular junction. Botulinium – toxin type A has been approved by the food and drug administration for use in painful orofacial and craniocervical muscle hyperactivity syndromes, including cervical dystonia and hemifacial spasm.



Figure(28): structure of botulinium toxin.

Most recently it has been shown helpful for chronic migraine problems that do not respond to medications, but this is an off – label use of this medication. There is much on going research on the efficacy of and indications for these injections for other conditions, including non spastic neuropathy and even trigeminal neuralgia. Evidence suggests that injections are best used for conditions where a clear cut muscle spasticity is present, the literature on botulinium toxin type A for non – spastic pain disorders is unconvincing. A review of literature examining preventative treatments for patients with chronic migraine or tension type headaches, including botulinium toxin injections, concluded that this agent has some efficacy for medication resistant chronic migraine sufferers but not for chronic tension – type – headache patients. Fortunately, there are relatively few significant adverse

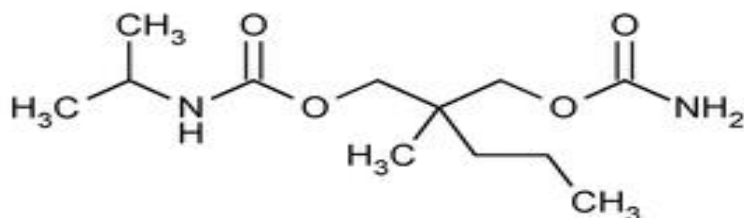
events seem with the use of botulinum – toxin type A in headache treatment. (Clarke 2013).

Drugs used for acute local muscle spasm:

1- Carisprodol:

It is CNS depressant. It has analgesic properties and to reduce local muscle spasm without significantly interfering with muscular or neuromuscular function. Its sedative qualities may also play a role in the muscle – relaxation – effect. It is short acting drug with minimal cumulative effect. Drug interactions are an additive sedative effect when taken with central nervous – system depressants such as alcohol or antihistamines.

Side effects: may include drowsiness, dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depression and insomnia.



Figure(29): structure of carisprodol

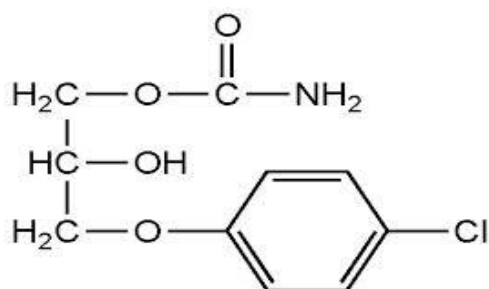
2- Chlorphenesin:

It is structurally and pharmacologically similar to metho – carbamol.

Its exact mechanism of action is unknown and its muscle relaxation effects are minimal. Its benefits are derived from its sedative effects.

It is used as an adjuvant in pain related to musculoskeletal – pain.

Side effects: include drowsiness and dizziness. Less common side- effects included confusion, insomnia, headache and nausea. Rash, fever or anaphylaxis are rare. It should not be given to patients with liver dysfunction.



Figure(30): structure of chlorophenesin.

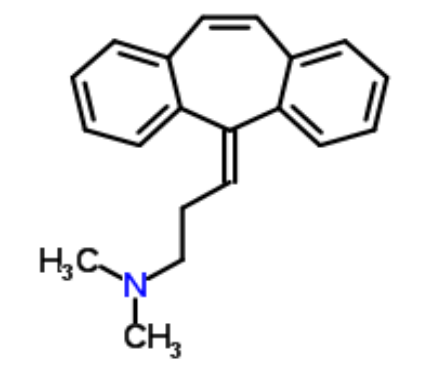
3-Chlorzoxazone:

It is a central – acting skeletal muscle relaxant with sedative qualities. It acts at the spinal cord level and sub – cortical areas of the brain, inhibiting reflex arcs that play a role in muscle spasm. In chronic pain it is administered orally.

Side effects: Gastro– intestinal disturbances, drowsiness, dizziness, light headedness, overstimulation and allergic skin rash. Serious reactions are extremely rare.

3-Cyclobenzaprine:

It is centrally – acting – muscle relaxant similar to the tricyclic – antidepressants. It relieves skeletal muscle spasm with the central nervous system at the brain – stem – level, although it may have an effect at the spinal cord level. It initially was studied for psychotherapeutic use with limited benefit and is more widely used for the relief of muscle spasm. It can be sedating, but does not appear to interfere with muscle function. Drowsiness is the most side – effects included dry mouth, dizziness, nausea, constipation, dyspepsia, tachycardia and urinary – retention.

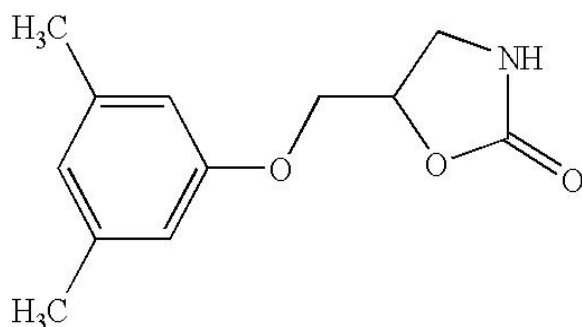


Figure(31): structure of cyclobenzaprine.

Metaxalone:

It is chemically similar to the mild tranquilizer, mephenoxalone. Its mode of action is unclear, but it is believed to cause muscle relaxation through depressing the central nervous system, and it has been used as an adjuvant therapy for many years in acute musculoskeletal conditions. It is absorbed rapidly with an onset of action about one hour after it is given.

Side effects: include nausea, vomiting, drowsiness, headache, nervousness, irritability, rash, and purities. Leukopenia, jaundice, and hemolytic anemia are extremely rare.



Figure(32): Structure of metaxalone

3-Methoxarbamol:

It is central – acting – skeletal muscle relaxant with a structure similar to mephenesin. It has been used in the United States for more than 40 years with success in treating acute musculoskeletal conditions. Its methods of action is not

clear, and it does not have a direct effect on strained muscle or the myoneural junction. In animals, it inhibits nerve signals in the internuncial neurons of the spinal cord and blocks polysynaptic reflexes.

Side – effects: usually improve with time and included light headness, vertigo, headache, blurred vision rash, flushing, gastro- intestinal upset, nasal congestion, and with the injectable form a metallic taste in the mouth.

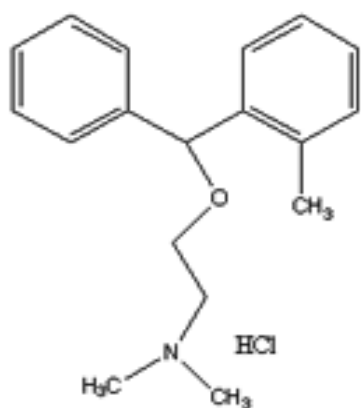
3-Orphenadrine:

It is centrally acting skeletal muscle relaxant with anticholinergic properties.

It is thought to work by relaxing skeletal muscles through blocking neuronal circuits where hyperactivity may play a role in hypertonia and spasm.

Many of the side effects: for orphenadrine are related to its anticholinergic effects and are related to dosage.

Potential side effects included tachycardia, palpitations, urinary retention, dry mouth, blurred vision, increased intra-ocular pressure, weakness, nausea, vomiting, headache and drowsiness.(C-David Tollison et al).



Orphenadrine Hydrochloride

Figure(33): structure of orphenadrine hydrochloride.

Neuromuscular Blocking drugs

a) Non-depolarizing Blocking drugs:

Isoquinoline derivatives:

1) Atracurium :

Biquaternary ammonium ester skeletal muscle relaxant.

Thus it reduces skeletal muscle relaxation for surgery or mechanical ventilation as adjunct to anesthesia.

It is better not to mix atracurium in some syringe or with lactated Ringer's injection and not to administer it through some IV needle as an alkaline solution such as barbiturate injection.

M.O.A:

It inhibits nerve impulse transmission by competing with acetylcholine for cholinergic receptors on motor-end-plate.

C.I.s:

Hypersensitivity to atracurium, its components or Benzyl alcohol.

Interactions:

Drugs:

Aminoglycosides, enflurance, furosemide, halothare, isoflurance, lithium, magnesium salts, polymyxin antibiotics, procainamide, quinidine, thiazide diuretics.

Possibly enhanced or prolonged effects of atracurium.

Opioid analgesics:

Possibly additive histamine release and increased risk and severity of bradycardia and hypotension.

Adverse Reactions:

CNS: seizures

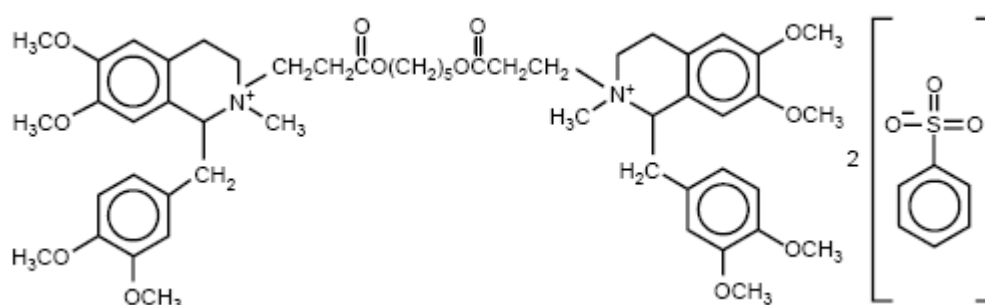
CV: Bradycardia, hypertension, hypotension, Tachycardia.

MS: Inadequate or prolonged neuromuscular blockade.

RESP: Apnea, bronchospasm, dyspnea, laryngospasm, wheezing.

Skin: Flushing, rash, urticaria.

Other: Anaphylaxis, injection site reaction (Jones and Bartlett Publishers).



Figure(34): structure of atracurium.

2) Cisatracurium :

It is one of the isomers of atracurium. It is about three times more potent than atracurium. The duration of action is longer than that of atracurium. It gives a degree of neuromuscular blockade. Cisatracurium and atracurium share the same metabolic pathways.

Laudanosine and a monognaternary acrylate are major metabolites of cisatracurium. Clinical problems of cisatracurium have not been observed due to histamine release after its administration.

CVS: NO C. V.S or Minor adverse effects were observed.

Immunologic: Anaphylactic Reations have been reported.

Renal disease: There was no difference in the duration of action of cisatracurium in patients with or without renal failure.

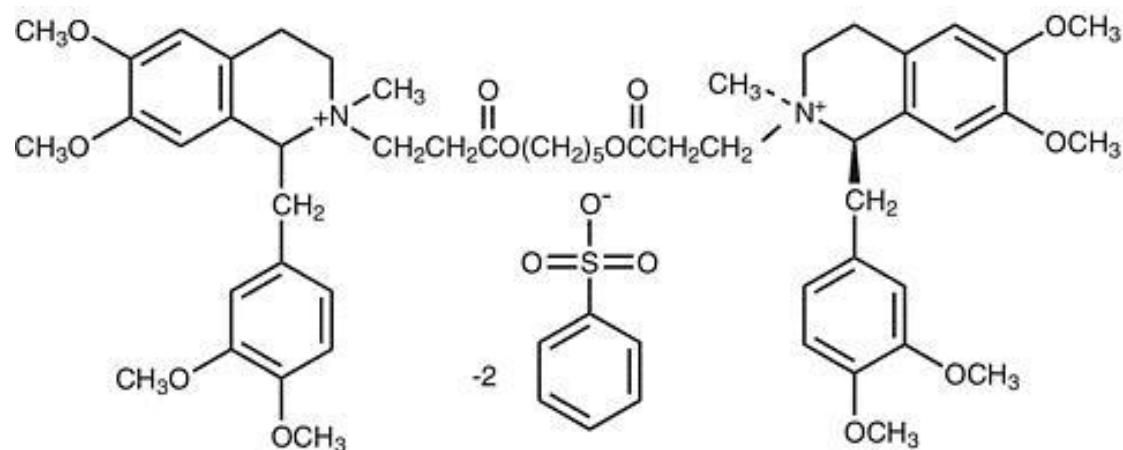
Age: Neither plasma clearance nor the duration of action of cisatracurium differed between young and elderly patients in elimination pathways.

Hepatic disease: Plasma clearance of cisatracurium reduced in patients with end-stage liver disease.

Drug-Drug-Interactions:

General Aenasthetics:

The action of cisatracurium is increased by isoklurane, sevoflurane and enflurane. (Aronson 2009).



Figure(35): structure of cisatracurium.

3) Doxacurium :

It is a bisquaternary benzyl isoquinolinium muscle relaxant. It is slowly hydrolyzed by plasma cholinesterase and mainly excreted unchanged in urine

and bile. It is the most potent N.M.B.D. available. It has in children a long onset of action even at high doses. It has a longer duration of action like D-tubocurarine or pancuronium (Mesetoja 2011).

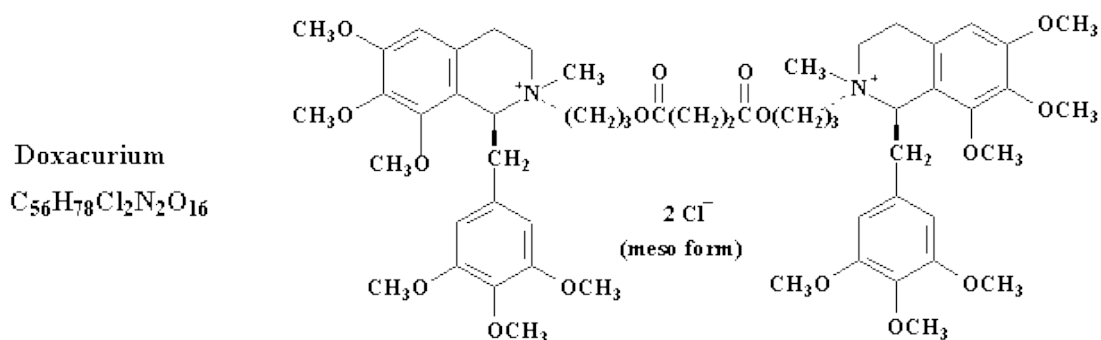
It is also a neuromuscular blocking drug or a skeletal-muscle-relaxant of non-depolarizing neuromuscular blocking drugs, to provide a skeletal-muscle relaxant during surgery or mechanical ventilation.

So it is used adjunctively in anesthesia.

It is also rarely used adjunctively to facilitate endotracheal intubation.

It is diester of succinic acid so it is a symmetrical molecule.

Trade name is Nuromax and is classified as a non-depolarizing long duration neuromuscular blocking agent. (. Current 2010).

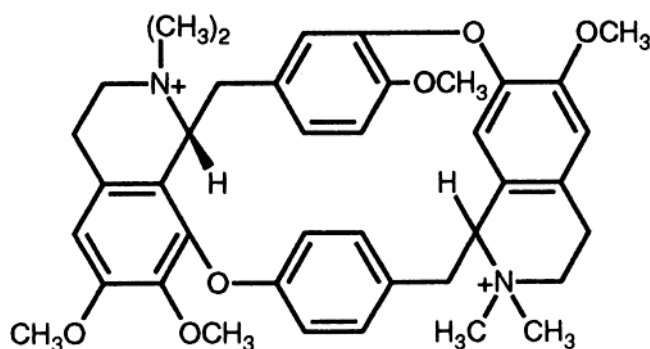


Figure(36): structure of doxacurium.

4) Metocurine :

It is a d-Tubocurarine analog, releases less histamine, C.I .in patients with iodide sensitivity and rarely used today in ICU or operating room. (R.A.ortega et al).

It is administrated intravenously and has long-duration of action. Only 1 % of the dose is demethylated in the liver and excreted unchanged in the urine and bile. (Fifer 2013).



Figure(37): structure of metocurine

5)Tubocurarine :

It is a skeletal muscle relaxant used as an adjunct to general anesthetics.

It is also used to diagnose Myasthenia-gravis. It is available for IV use only.

Up to 75% of tubocurarine in the first 24 hours is excreted unchanged by the kidneys. Another 11 % may undergo biliary excretion. Only a small amount is metabolized. It crosses the placenta and entering breast milk is unknown.

It is found in certain plants in the Amazon rain forest.

It is an antagonist of Acetylcholine, competing with the Neurotransmitter for the cholinergic receptor site at the motor-end-plate.

This antagonism decreases the response of the muscle to Acetylcholine, causing a relaxed paralysis.

It doesn't cross the Blood-Brain-Barrier and thus has no action on the CNS.

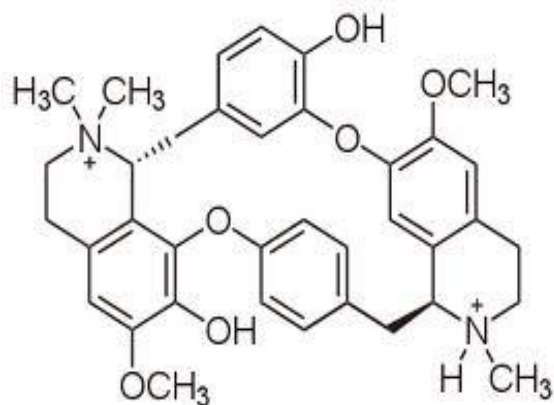
It is C.I in pts who have shown hypersensitivity to the drug and also CI for use in early pregnancy as it causes teratogenic effects.

It is used with caution in patients who already have got pulmonary disease or lung cancer, which may lead to enhanced neuromuscular blockade, also used in caution with patients having myasthenia gravis, and in patients with decreased renal function as Tubocurarine is excreted unchanged by the kidneys.

S.E.s:

Patients may respond to their first exposure to tubocurarine with hypersensitivity reaction or hyperthermia which is muscle contraction,

elevated body temperature, severe acidosis and if the reaction is uncontrolled, this may lead to death (Venable 2009).



Figure(38): structure of tubocurarine

5) **Mivacurium :**

It is a benzlisoquinoline derivative with a short duration of action.

It is hydrolysed by plasma cholinesterase like succinylcholine. It produces non-depolarizing blockade.

S.E.s:

Like atracurium, mivacurium releases histamine.

Hypotension, Tachycardia, erythema and flushing. (Donati 2009).

It is also used to facilitate intubation and controlled ventilation.

It acts by competitive antagonism of Acetylcholine at nicotinic (N₂) receptors at the postsynaptic membrane of the neuromuscular junction.

It is administrated by IV injection.

It has minimal C.V. effects, a slight decrease in BP and slight increase in heart rate may occur after rapid intravenous injection.

It has no vagal or ganglian blocking properties in the normal dosage range (Smith 2011).

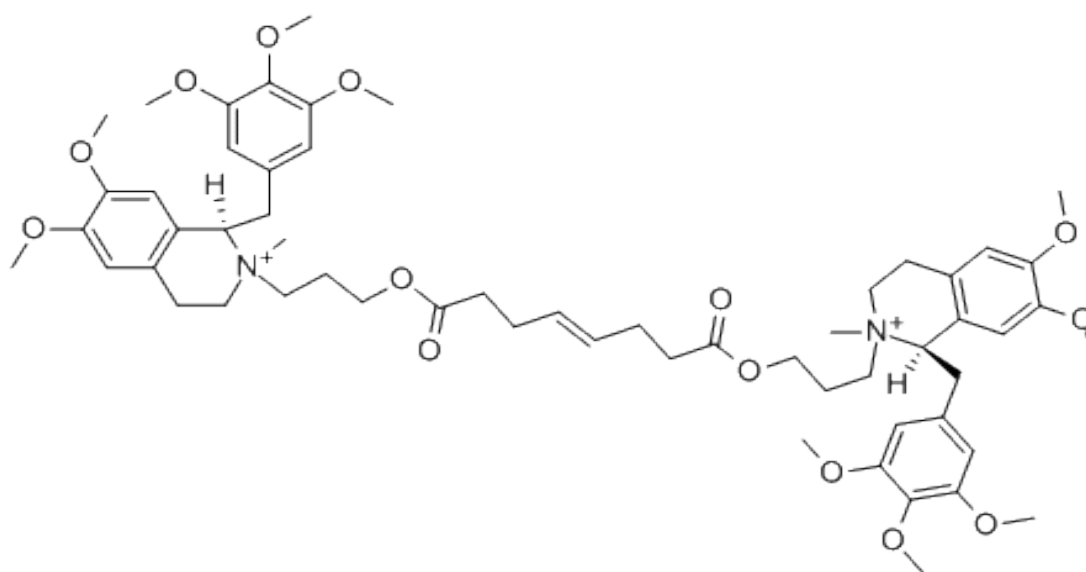


Figure (39): structure of mivacurium.

2- Neuromuscular blocking drugs:

(a) Non - depolarizing – blocking – drugs:

Steroid – derivatives:

1- pancuronium:-

It is a bisquaternary aminosteroid that was introduced in 1967 and is a chemical derivative of malouetin (a plant alkaloid from the perwinkle family with neuromuscular blocking activity). It is a non-depolarizing neuromuscular blocker, skeletal-muscle-relaxant. It is C.I in patients having hypersensitivity to bromides, in patients with tachycardia, and even in those having a minor increase in heart rate. It is used cautiously in patients with respiratory depression, myasthenia gravis, dehydration, thyroid disorders, hyperthermia, renal, hepatic or pulmonary impairment, in elderly in pregnant women and in breast feeding women.

Adverse-Reactions:

C.V.: increase blood Pressure, Tachycardia

EENT: excessive salivation.

musculo skeletal: residual – muscle weakness.

Respiratory: prolonged, dose-related respiratory insufficiency or apnea, wheezing.

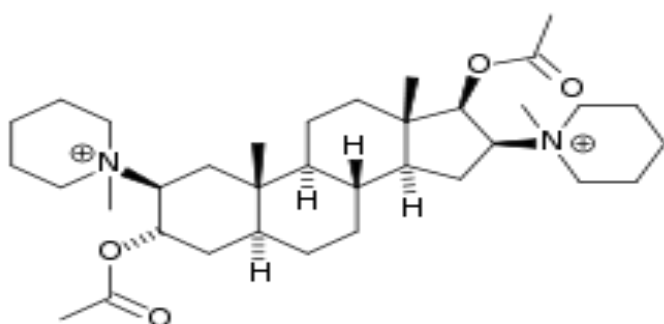
Skin: excessive diaphoresis, transient rashes.

Other: allergic or idiosyncratic hypersensitivity reactions, burning sensation.

Interactions:**Drug-drug:**

- Amikacin, gentamicin, neomycin, streptomycin, tobramycin: may increase the effects of non-depolarizing muscle relaxant, including prolonged respiratory depression.
- Carbamazepine, phenytoin: may decrease the effects of pancuronium causing it to be less effective.
- Clindamycin, general anaesthetics, kanamycin, quinidine, ketamine, polymyxin antibiotics such as polymyxin, B sulfate:- may increase neuromuscular blockage leading to an increase in skeletal muscle relaxation, and prolonged effect.
- Lithium, opioid analgesics, verapamil :- may increase, neuromuscular blockade leading to an increase in skeletal – muscle – relaxation and respiratory paralysis.
- Succinylcholine: may increase duration and intensity of blockade.
- Theophylline: may reverse the neuromuscular blocking effects of pancuronium.

- **Pharmacokinetics:**
- Absorption: given I.V.
- Distribution: about 87% bound to plasma proteins.
- Metabolism: unknown
- Excretion: mainly in urine, some biliary.
- Half – life: about 2 hours. (Kluwer 2009)



Figure(40): structure of pancuronium.

2 – Pipercuronium:

It is a bisquaternary – compound. It was available in Eastern Europe for many years and now become available in the west. Its onset and duration of action are similar to those of pancuronium. It has a longer duration of action. It is lack of C.V. side effects. It is eliminated slowly and mainly through the kidney .(Mirakhur 2003,).

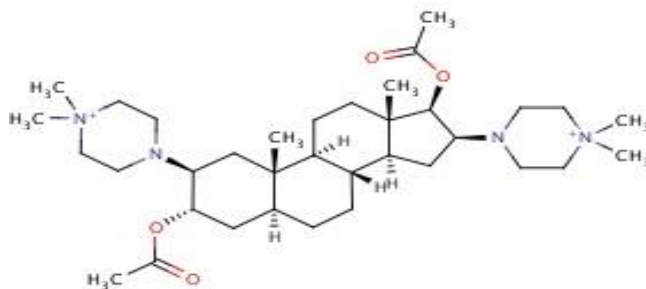
Drug – Drug Interaction:

- Barbiturates: Thiobutobarbital prolongs the duration of action of pipercuronium in dogs, but no interaction with barbiturates in man has been reported.
- General anaesthetics: when small doses of pipercuronium are given , the duration of blockade is significantly longer during isoflurane

anesthesia than during neuroleptanesthesia , halothane is also associated with a Prolonged action but to a lesser Extent.

Organs and systems:-

- C.v.: no histamine release has been reported with pipercuronium.
Rarely significant hypotension has been reported bradycardia has also been seen but is usually mild.
No signification changes in heart rate or blood pressure are seen.
The absence of tachycardia in these high – risk cardiac patients, in whom an increase in myocardial $-O_2-$ demand is unwanted, was considered an advantage of pipercuronium. (Aronson 2009)



Figure(41): Structure of pipercuronium

3- Rocuronium:

it is a steroidal agent related chemically to Vecuronium and has a quicker onset of action.

The plasma clearance of rocuronium is primarily due to liver uptake and biliary excretion.

About one-third of an injected dose is excreted unchanged in the urine.

* Organs And Systems:-

- **C.v.:** it has no c.v. adverse effects. Minor increases in heart rate can occur with higher doses.

There are several reports of pain during injection of rocuronium.

- **Immunologic:** several- allergic reactions to rocuronium have been reported.

- **Susceptibility factors:**

- **Age:** in elderly patients, the duration of action of Rocuronium can be prolonged because of reduced hepatic elimination

- **Hepatic disease:** the duration of action of rocuronium was significantly prolonged in patients with liver cirrhosis, which might be explained by a lower plasma clearance.

- **Drug-Drug-interactions:-**

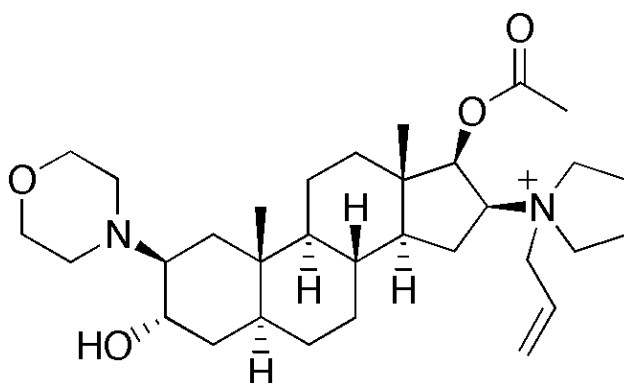
- **Anticonvulsant-drugs:**

The duration of action of Rocuronium can be reduced during long-term therapy with anticonvulsants.

It was suggested that the dose of rocuronium should be increased in patients taking antiepileptic drugs

- **General anaesthetics:**

The neuromuscular blocking effects of rocuronium are potentiated by halothane, enflurane, and isoflurane (Aronson 2009).



Figure(42): structure of rocuronium

4-Vecuronium:

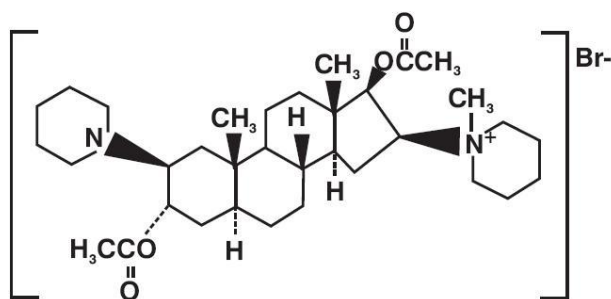


Figure (43): structure of vecuronium.

it is a monoquaternary neuromuscular blocker with an intermediate duration of action. It is a steroidal relaxant to pancuronium, is taken up largely by the liver then excreted unchanged via hepatobiliary system or excreted through the kidneys.

It is characterized by:

- 1- A slight decrease in potency.
- 2- Virtual loss of the vagolytic Properties of pancuronium,
- 3- Molecular instability in solution (this explains the shorter duration of action of vecuronium compared with pancuronium) and
- 4- Increased lipid solubility, which results in a greater biliary elimination of vecuronium than pancuronium.

It is mainly excreted by the liver and about 30% renal excretion. It is prepared as a lyophilized powder because it is less stable in solution. (MASHOUR 2011) .

- **The reasons of popularity of vecuronium are:-**

- (i) it helps in more facile tracheal intubation
- (ii) it causes easy administration by infusion for maintenance.
- (iii) it possesses intermediate duration of action.
- (iv) it has faster and more complete recovery
- (v) it causes a remarkable lack of cardiovascular side effect.

It has two major routes of elimination, the liver and the kidney, they are of approximately equal importance. (Agasti 2011)

b- Depolarizing drugs:

- **Succinylcholine: (succinylcholine)**

It is the paralytic of choice because of its rapid onset, short duration, and reliable pharmacodynamic profile. It provides neuromuscular blockade by irreversibly binding to nicotinic muscle receptors thus maintaining the motor end plate in a state of constant depolarization, thus it causes muscle relaxation, leading to paralysis until it dissociates from the receptors.

Side- effects:-

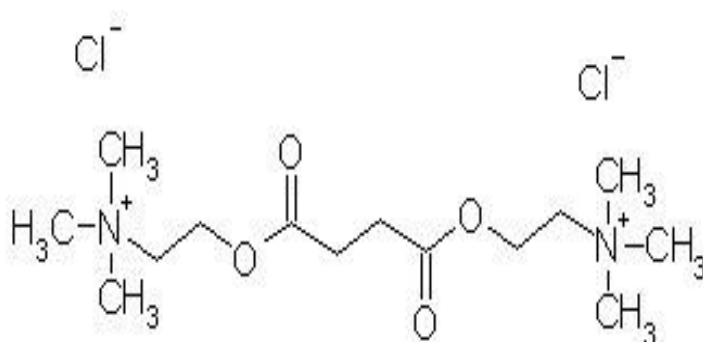
Muscle pain, muscle breakdown, hyperkalemia, and hypertension, it increases intraocular pressure and should not be used in patient with eye injury and glaucoma.

It rarely can lead to bradycardia.

Due to its side effects, rocuronium and rapacuronium are used as alternatives to succinylcholine .

(Galvagno 2003).

Absorption, Metabolism and Excretion: it is given systemically because it doesn't easily cross membranes. It is rapidly hydrolyzed by plasma cholinesterase which is synthesized in the liver to succinylmonocholine, which is pharmacologically inactive. About 10% of succinylcholine is excreted unchanged in the urine. (Miyamoto 2004).



Figure(44): structure of succinylcholine.

Summary

Antispasmodic or spasmolytic agent is a drug or a herb that suppresses muscle contractions, called spasms.

Humans have smooth and skeletal muscles, thus, requiring different medications for controlling spasms.

Smooth muscles for example include the muscle of gut and intestines, antimuscarinics are used to treat smooth muscle spasms acting as a competitive inhibitor of muscarinic receptors at smooth muscles.

Common medications include atropine and hyoscyamine.

Herbs also used to treat smooth muscle spasms e.g. peppermint oil and mebeverine.

Skeletal muscles are connected to bones, and allow joints to move voluntarily.

Antispasmodic agents used to treat these muscles, including cyclobenzaprine, tizanidine, and baclofen.

They work by mediating nerve signal messages that normally control muscle movement.

Some of the common side effects of spasmolytic drugs are drowsiness, dizziness, gastro-intestinal disturbances or insomnia.

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