SECTION 6

DRUGS ACTING ON PERIPHERAL (SOMATIC) NERVOUS SYSTEM

Chapter 25 Skeletal Muscle Relaxants

Skeletal muscle relaxants are drugs that act peripherally at neuromuscular junction/muscle fibre itself or centrally in the cerebrospinal axis to reduce muscle tone and/or cause paralysis. The neuromuscular blocking agents are used primarily in conjunction with general anaesthetics to provide muscle relaxation for surgery, while centrally acting muscle relaxants are used mainly for painful muscle spasms and spastic neurological conditions.

PERIPHERALLY ACTING MUSCLE RELAXANTS

I. Neuromuscular blocking agents

A. Nondepolarizing (Competitive) blockers

1. *Long acting*: d-Tubocurarine, Pancuronium, Doxacurium, Pipecuronium
2. *Intermediate acting:* Vecuronium, Atracurium, Cisatracurium, Rocuronium, Rapacuronium
3. *Short acting:* Mivacurium

B. Depolarizing blockers

Succinylcholine (SCh., Suxamethonium), Decamethonium (C-10)

II. Directly acting agents

Dantrolene sodium
Quinine

Note: 1. Decamethonium is not used clinically.

2. Aminoglycoside, tetracycline, polypeptide antibiotics interfere with neuromuscular transmission at high doses, but are not employed as muscle relaxants.

NEUROMUSCULAR BLOCKING AGENTS

Curare It is the generic name for certain plant extracts used by south American tribals as arrow poison for game hunting. The animals got paralysed even if not killed by the arrow. Natural sources of curare are *Strychnos toxifera, Chondrodendron tomentosum* and related plants. Muscle paralysing active principles of these are tubocurarine, toxiferins, etc.

Tubocurarine was first clinically used in 1930s; many synthetic compounds including *Succinylcholine* were introduced subsequently. Search has continued for neuromuscular blockers to provide greater cardiovascular stability during surgery and for drugs with differing onset and duration of action to suit specific requirements. The latest additions are *doxacurium, pipecuronium, rocuronium, mivacurium, rapacuronium* and *cisatracurium.*

MECHANISM OF ACTION

The site of action of both competitive and depolarizing blockers is the end plate of skeletal muscle fibres.

Competitive block (Nondepolarizing block)

This is produced by curare and related drugs. Claude Bernard (1856) precisely localized the site of action of curare to be the neuromuscular junction. He stimulated the sciatic nerve of pithed frog and recorded the contractions of gastrocnemius muscle. Injection of curare in the ventral lymph sac caused inhibition of muscle twitches but there was no effect if the blood supply of the hind limb was occluded. This showed that curare acted peripherally and not centrally. Soaking a portion of the sciatic nerve in curare solution did not affect the twitches and a curarized muscle still responded to direct stimulation—thus, nervous conduction and muscle contraction were intact. The only possible site of action could be the neuromuscular junction. This has now been confirmed by close iontophoretic application of d-TC to the muscle end plate and by other modern techniques.

The competitive blockers have affinity for the nicotinic (N_M) cholinergic receptors at the muscle end plate, but have no intrinsic activity. The N_M receptor has been isolated and studied in detail. It is a protein with 5 subunits ($\alpha 2\ \beta\ \varepsilon$ or γ and δ) which are arranged like a rosette surrounding the Na^+ channel (*see* Fig. 4.4). The two α subunits carry two ACh binding sites; these have negatively charged groups which combine with the cationic head of ACh → opening of Na^+ channel. Most of the competitive blockers have two or more quaternary N^+ atoms (Fig. 25.1) which provide the necessary attraction to the same site, but the bulk of the antagonist molecule does not allow conformational changes in the subunits needed for opening the channel. Competitive blockers generally have thick bulky molecules and were termed *Pachycurare* by Bovet (1951). ACh released from motor nerve endings is not able to combine with its receptors to generate end plate potential (EPP). d-TC thus reduces the frequency of channel opening but not its duration or the conductance of a channel once it has opened. When the magnitude of EPP falls below a critical level, it is unable to trigger propagated muscle action potential (MAP) and

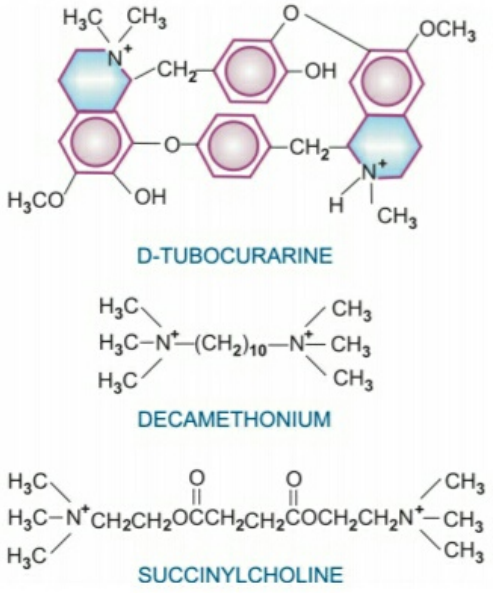

Fig. 25.1: Chemical structure of three neuromuscular blockers. Note the thick, bulky molecule of competitive blocker d-tubocurarine and slender, flexible molecules of depolarizing blockers decamethonium and succinylcholine

muscle fails to contract in response to nerve impulse. The antagonism is surmountable by increasing the concentration of ACh *in vitro* and by anticholinesterases *in vivo*. At very high concentrations, curare like drugs enter the Na^+ channels and directly block them to produce more intense noncompetitive neuromuscular block that is only partly reversed by neostigmine.

The competitive blockers also block prejunctional nicotinic receptors located on motor nerve endings. Since activation of these receptors by ACh normally facilitates mobilization of additional quanta of ACh from the axon to the motor nerve endings, their blockade contributes to depression of neuromuscular transmission. Accordingly, the competitive blockers exhibit the 'fade' phenomenon (Fig. 25.3), i.e. twitch responses during partial block are progressively depressed on repetitive stimulation.

Tetanic stimulation during partial nondepolarizing block increases the response to a subsequent single stimulation (twitch). This is called *'post-tetanic potentiation'*, and is probably due

to a transient increase in prejunctional ACh mobilization following tetanic stimulation.

Depolarizing block Decamethonium and SCh have affinity as well as submaximal intrinsic activity at the N_M cholinoceptors. They depolarize muscle end plates by opening Na^+ channels (just as ACh does) and initially produce twitching and fasciculations. Because in the focally innervated mammalian muscle, stimulation is transient; longer lasting depolarization of muscle end plate produces repetitive excitation of the fibre. In the multiplely innervated contracture muscle (rectus abdominis of frog) stimulation is prolonged resulting in sustained contraction. These drugs do not dissociate rapidly from the receptor and are not hydrolysed by AChE. They induce prolonged partial depolarization of the region around muscle end plate → Na^+ channels get inactivated (because transmembrane potential drops to about –50 mV) → ACh released from motor nerve endings is unable to generate propagated MAP → flaccid paralysis in mammals. In other words a zone of inexcitability is created around the end plate preventing activation of the muscle fibre. In birds, the area of depolarization is more extensive and spastic paralysis occurs.

Depolarizing blockers also have 2 quaternary N^+ atoms, but the molecule is long, slender and flexible—termed *Leptocurare* by Bovet. The features of classical depolarizing block differ markedly from that of nondepolarizing block (*see* Fig. 25.2 and Table 25.1).

However, in many species, e.g. dog, rabbit, rat, monkey, in slow contracting soleus muscle of cat, and under certain conditions in man the depolarizing agents injected in high doses or infused continuously produce dual mechanism neuromuscular blockade which can be divided into two phases:

Phase I block It is rapid in onset, results from persistent depolarization of muscle end plate and has features of classical depolarization blockade. This depolarization declines shortly afterwards and repolarization occurs gradually despite continued presence of the drug at the receptor, but neuromuscular transmission is not restored and phase II block supervenes.

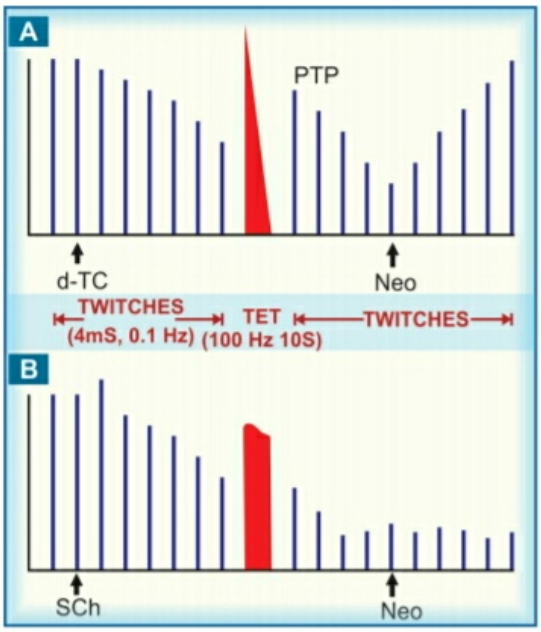

Fig. 25.2: Illustration of characteristics of competitive (A) and depolarizing (B) neuromuscular blockade in sciatic nerve-gastrocnemius muscle of cat
A. Tubocurarine (d-TC) produces progressive decrease in twitch tension; tetanic stimulation (TET) produces poorly sustained contracture, which is followed by post-tetanic potentiation (PTP); Neostigmine (Neo) restores the twitch contractions.
B. Succinylcholine (SCh) produces initial augmentation of twitches followed by progressive block; tetanus is well sustained, but there is no PTP; block is not reversed (rather worsened) by neostigmine.

Phase II block It is slow in onset and results from desensitization of the receptor to ACh. It, therefore, superficially resembles block produced by d-TC. The muscle membrane is nearly repolarized, recovery is slow, contraction is not sustained during tetanic stimulation ('fade' occurs) and the block is partially reversed by anticholinesterases.

In man and fast contracting muscle (tibialis anterior) of cat, normally only phase I block is seen. Phase II block may be seen in man when SCh is injected in high dose or infused

TABLE 25.1 Features of competitive and typical depolarizing block

		Competitive block (d-TC)	*Depolarizing (phase I) block (SCh)*
1.	Paralysis in man	Flaccid	Fasciculations → flaccid
2.	Paralysis in chick	Flaccid	Spastic
3.	Effect on isolated frog's rectus muscle	No contraction, antagonism of ACh	Contraction
4.	Species sensitivity	Rat > rabbit > cat	Cat > rabbit > rat
5.	Human neonates	More sensitive	Relatively resistant
6.	Tetanic stimulation during partial block	Poorly sustained contraction	Well sustained contraction
7.	Neostigmine	Antagonises block	No effect
8.	Post tetanic potentiation	Present	Absent
9.	Ether anaesthesia	Synergistic	No effect
10.	Order of paralysis	Fingers, eyes → limbs → neck, face → trunk → respiratory	Neck, limbs → face, jaw, eyes, pharynx → trunk → respiratory
11.	Effect of lowering temperature	Reduces block	Intensifies block
12.	Effect of cathodal current to end plate	Lessens block	Enhances block

continuously, particularly, if fluorinated anaesthetics have been used. SCh readily produces phase II block in patients with atypical or deficient pseudocholinesterase.

ACTIONS

1. Skeletal muscles Intravenous injection of nondepolarizing blockers rapidly produces muscle weakness followed by flaccid paralysis. Small fast response muscles (fingers, extraocular) are affected first; paralysis spreads to hands, feet—arm, leg, neck, face—trunk—intercostal muscles—finally diaphragm: respiration stops. The rate of attainment of peak effect and the duration for which it is maintained depends on the drug (Table 25.2), its dose, anaesthetic used, haemodynamic, renal and hepatic status of the patient and several other factors. Recovery occurs in the reverse sequence; diaphragmatic contractions resume first. In general, the more potent nondepolarizing blockers have a longer onset of action.

Depolarizing blockers typically produce fasciculations lasting a few seconds before inducing flaccid paralysis, but fasciculations are not prominent in well-anaesthetized patients. Though the sequence in which muscles are involved is somewhat different from the competitive blockers (Table 25.1), the action of SCh develops with such rapidity that this is not appreciated. Apnoea generally occurs within 45–90 sec, but lasts only 2–5 min; recovery is rapid.

Clinical monitoring of neuromuscular block

In anaesthetic practice neuromuscular block (especially during recovery) is monitored by recording contractile responses of thumb muscles to transcutaneous ulnar nerve stimulation. Since single twitch responses have to be interpreted in comparison to twitches before the blocker, and are not reliable, several other protocols are used. One such method is 'train-of-four' (TOF) protocol. Four supramaximal electrical stimuli are applied in 2S (2Hz) and contractions of thumb muscle are recorded (Fig. 25.3A). The TOF-ratio is obtained by dividing the strength of 4th contraction by that of the 1st. In the untreated subject all the 4 contractions remain equal and TOF-ratio is 1.0.

During partial competitive block (as during onset and recovery or reversal) the degree of block corresponds to the decrease in TOF-ratio, because competitive blockers exhibit 'fade' phenomenon. As the muscles recover, the TOF-ratio improves and becomes 1.0 at complete recovery.

On the other hand, classical or phase-I depolarizing block does not exhibit fade; the TOF-ratio remains 1.0, though all the 4 twitches are depressed equally depending on the degree of block. Fade is again seen when phase II or desensitization

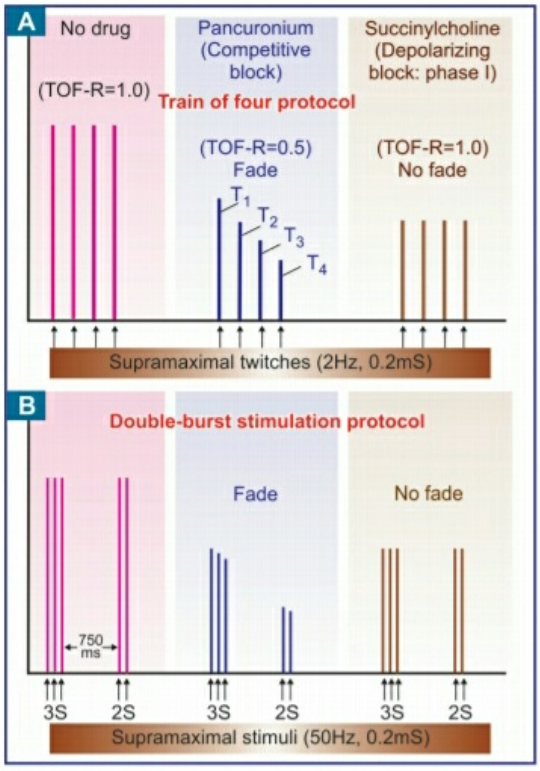

Fig. 25.3: Clinical assessment of neuromuscular block. (A) *Train-of-four (TOF) protocol:* Contractile responses of adductor pollicis muscle to transcutaneous ulnar nerve stimulation with train-of-four protocol of impulses during recovery of neuromuscular block. TOF-R—Train of four ratio (strength of 4th contraction divided by that of the 1st). (B) *Double-burst stimulation ($DBS_{3,2}$):* Evoked responses to burst of three 0.2 ms pulses at 50 Hz followed 750 ms later by a second burst of two similar pulses. Note 'fade' in the second burst after nondepolarizing block.

block occurs with prolonged use of a depolarizing agent and TOF-ratio is depressed as in the case of competitive block. However, SCh generally requires no monitoring.

Rather than measuring each contraction and calculating TOF ratio, in practice, it is easier to simply observe the disappearance (during onset) or reappearance (during recovery) of the successive twitches. Reappearance of 2nd twitch (T_2) corresponds to ~10% recovery (~90% residual block) and that of 4th twitch (T_4) to ~25% recovery.

Because fade is more prominent during sustained stimulation, an alternate method is 'tetanic stimulation' protocol, in which 0.2 ms pulses are applied at 50–100 Hz for 4–5 seconds and presence or absence of fade is noted (*see* fade in Fig. 25.2A).

Many anaesthesiologists prefer to use the less painful variant of tetanic stimulation, *viz* 'double-burst stimulation' (DBS). A burst of three 0.2 ms pulses at 50 Hz is followed after a gap of 750 ms by a second burst of 2 or 3 similar pulses (Fig. 25.3B). The strength of response during the 2nd burst relative to the first is a measure of the recovery from block.

Measurement of 'post-tetanic count (PTC)' is another clinically used method.

2. Autonomic ganglia Because the cholinergic receptors in autonomic ganglia are nicotinic (though of a different subclass N_N), competitive neuromuscular blockers produce some degree of ganglionic blockade; d-TC has the maximum propensity in this regard, while the newer drugs (vecuronium, etc.) are practically devoid of it. SCh may cause ganglionic stimulation by its agonistic action on nicotinic receptors.

3. Histamine release d-TC releases histamine from mast cells. This does not involve immune system and is due to the bulky cationic nature of the molecule. Histamine release contributes to the hypotension produced by d-TC. Flushing, bronchospasm and increased respiratory secretions are other effects. Intradermal injection of d-TC produces a wheal similar to that produced by injecting histamine. Histamine releasing potential of other neuromuscular blockers is graded in Table 25.2.

Heparin may also be simultaneously released from mast cells.

4. C.V.S.

d-Tubocurarine produces significant fall in BP. This is due to—

(a) ganglionic blockade
(b) histamine release and
(c) reduced venous return—a result of paralysis of limb and respiratory muscles.

Heart rate may increase due to vagal ganglionic blockade. Pancuronium and vecuronium also tend to cause tachycardia. All newer nondepolarizing drugs have negligible effects on BP and HR.

Cardiovascular effects of SCh are variable. Generally bradycardia occurs initially due to activation of vagal ganglia followed by tachycardia and rise in BP due to stimulation of sympathetic ganglia. BP occasionally falls on account of its muscarinic action causing

TABLE 25.2 Comparative properties of neuromuscular blocking drugs

Drug	Dose£ (mg/kg)	Onset* (min)	Duration@ (min)	Hist. release	Gang. block	Vagal block
LONG ACTING						
1. d–Tubocurarine	0.2–0.4	4–6	30–60	+++	++	±
2. Pancuronium	0.04–0.1	4–6	60–120	±	±	+
3. Doxacurium	0.03–0.08	4–8	60–120	+	–	–
4. Pipecuronium	0.05–0.08	2–4	50–100	±	–	–
INTERMEDIATE ACTING						
5. Vecuronium	0.08–0.1	2–4	30–60	±	–	±
6. Atracurium	0.3–0.6	2–4	20–40	+	–	–
7. Cisatracurium	0.15–0.2	3–6	20–40	–	–	–
8. Rocuronium	0.6–0.9	1–2	25–40	–	–	±
SHORT ACTING						
9. Mivacurium	0.15–0.2	2–4	15–30	+	–	–
10. Succinylcholine	0.5–0.8	1–1.5	5–8	++	St.	St.

£ Initial paralysing dose for opioid/nitrous oxide + oxygen anaesthesia. In patients anaesthetised with ether/halothane/isoflurane, the dose may be $^1/_3$–$^1/_2$ of the figure given.

* Time to maximal block after i.v. injection.

@ Duration of surgical grade relaxation after usual clinical doses; time to 95% recovery of muscle twitch is nearly double of the figure given (especially for long-acting drugs). Duration is dose dependent as well.

St.—Stimulation

vasodilatation. Prolonged administration of SCh has caused cardiac arrhythmias and even arrest in patients with burns, soft tissue injury and tetanus. Efflux of intracellular K^+ occurs in these conditions which is augmented by prolonged depolarization of skeletal muscles.

5. G.I.T. The ganglion blocking activity of competitive blockers may enhance postoperative paralytic ileus after abdominal operations.

6. C.N.S. All neuromuscular blockers are quaternary compounds—do not cross blood-brain barrier. Thus, on i.v. administration no central effects follow. However, d-TC applied to brain cortex or injected in the cerebral ventricles produces strychnine like effects.

PHARMACOKINETICS

All neuromuscular blockers are polar quaternary compounds—not absorbed orally, do not cross cell membranes, have low volumes of distribution and do not penetrate placental or blood-brain barrier. They are practically always given i.v., though i.m. administration is possible. Muscles with higher blood flow receive more drug and are affected earlier. Redistribution to non-muscular tissues plays a significant role in the termination of surgical grade muscle relaxation, but residual block may persist for a longer time depending on the elimination t½. The duration of action of competitive blockers is directly dependent on the elimination t½. Drugs that are primarily metabolized in the plasma/liver, e.g. vecuronium, atracurium, cisatracurium, rocuronium, and especially mivacurium have relatively shorter t½ and duration of action (20–40 min), while those largely excreted by the kidney, e.g. pancuronium, d-Tc, doxacurium and pipecuronium have longer t½ and duration of action (>60 min). With repeated administration redistribution sites are filled up and duration of action is prolonged.

The unchanged drug is excreted in urine as well as in bile.

SCh is rapidly hydrolysed by plasma pseudocholinesterase to succinylmonocholine and then succinic acid + choline (action lasts 5–8 min). Some patients have genetically determined abnormality (low affinity for SCh) or deficiency of pseudocholinesterase. In subjects who are homozygous for the abnormal enzyme (1 in > 3000 population), SCh causes prolonged phase II blockade resulting in muscle paralysis and apnoea lasting 4–6 hours, because SCh is a poor substrate for the more specific AChE found at the motor end plate. However, duration of paralysis is increased only by 2–3 times in subjects who are heterozygous for the abnormal enzyme (1 in ~ 50), or have only relative deficiency. The prolonged apnoea can be tided over only by mechanical ventilation.

NOTES ON INDIVIDUAL COMPOUNDS

1. d-Tubocurarine Because of its prominent histamine releasing, ganglion blocking and cardiovascular actions as well as long duration of paralysis needing pharmacological reversal, d-TC is not used now.

2. Succinylcholine Despite its propensity to cause muscle fasciculations and soreness, changes in BP and HR, arrhythmias, histamine release and K^+ efflux from muscles causing hyperkalaemia and its complications, SCh is the most commonly used muscle relaxant for passing tracheal tube. It induces rapid, complete and predictable paralysis with spontaneous recovery in ~5 min. Excellent intubating condition *viz.* relaxed jaw, vocal cords apart and immobile with no diaphragmatic movements, is obtained within 1–1.5 min. Occasionally SCh is used by continuous i.v. infusion for producing controlled muscle relaxation of longer duration. It should be avoided in younger children unless absolutely necessary, because risk of hyperkalaemia and cardiac arrhythmia is higher. Risk of regurgitation and aspiration of gastric contents is increased by SCh in GERD patients and in the obese, especially if stomach is full.

MIDARINE, SCOLINE, MYORELEX, ENTUBATE 50 mg/ml inj, 2 ml amp.

3. Pancuronium A synthetic steroidal compound, ~5 times more potent and longer acting than d-TC; provides good cardiovascular stability (little ganglionic blockade), seldom induces flushing, bronchospasm or cardiac arrhythmias because of lower histamine releasing potential. Rapid i.v. injection may cause rise in BP and tachycardia due to vagal blockade and NA release. It is primarily eliminated by renal excretion. Because of longer duration of action, needing reversal, its use is now restricted to prolonged operations, especially neurosurgery.

PAVULON, PANURON, NEOCURON 2 mg/ml in 2 ml amp.

4. Doxacurium A bisquaternary muscle relaxant having the least rapid onset and the longest action: suitable for long duration surgeries. It is primarily eliminated by kidney, though hepatic metabolism also occurs. Cardiovascular changes are less marked.

5. Pipecuronium Another muscle relaxant with a slow onset and long duration of action; steroidal in nature; recommended for prolonged surgeries. It exerts little cardiovascular action, though transient hypotension and bradycardia can occur. Elimination occurs through both kidney and liver.

ARDUAN 4 mg/2 ml inj.

6. Vecuronium A close congener of pancuronium with a shorter duration of action due to rapid distribution and metabolism. It is excreted mainly in bile, recovery is generally spontaneous, but may need neostigmine reversal. Cardiovascular stability is still better due to lack of histamine releasing and ganglionic action; tachycardia sometimes occurs. Currently, it is the most commonly used muscle relaxant for routine surgery and in intensive care units.

NORCURON 4 mg amp, dissolve in 1 ml solvent supplied.
NEOVEC 4 mg amp, 10 mg vial.

7. Atracurium A bisquaternary competitive blocker, 4 times less potent than pancuronium and shorter acting: reversal is mostly not required. The unique feature of atracurium is inactivation in plasma by spontaneous non-enzymatic degradation (Hofmann elimination) in addition to that by cholinesterases. Consequently its duration of action is not altered in patients

with hepatic/renal insufficiency or hypodynamic circulation. It is the preferred muscle relaxant for liver/kidney disease patients as well as for neonates and the elderly. Hypotension may occur due to dose dependent histamine release.

TRACRIUM 10 mg/ml inj in 2 ml vial.

8. Cisatracurium This *R-Cis, R-Cis* enantiomer of atracurium is nearly 4 times more potent, slower in onset, but similar in duration of action. Like atracurium it undergoes Hofmann elimination, but in contrast it is not hydrolysed by plasma cholinesterase. Most importantly, it does not provoke histamine release.

Side effects are fewer.

9. Rocuronium A newer nondepolarizing blocker with a rapid onset and intermediate duration of action which can be used as alternative to SCh for tracheal intubation without the disadvantages of depolarizing block and cardiovascular changes. The same drug also serves as maintenance muscle relaxant, seldom needing reversal. The onset of action is dose-dependent; intubating conditions are attained in 90 sec with 0.6 mg/kg, but within 60 sec at 1.0 mg/kg. Within limits, the duration of paralysis is also dose-dependent. This neuromuscular blocker is gaining popularity for its versatility and more precisely timed onset and duration of action. Infused i.v. (0.3–0.6 mg/kg/hour), it is also being used to facilitate mechanical ventilation in intensive care units. Though little metabolized, it is eliminated mainly in bile. Mild vagolytic action increases HR somewhat.

ROCUNIUM, CUROMID 50 mg/5 ml, 100 mg/10 ml vials.

10. Mivacurium It is the shortest acting competitive blocker; does not need reversal. Dose and speed of injection related transient cutaneous flushing can occur due to histamine release. Fall in BP is possible, but change in HR is minimal. It is metabolized rapidly by plasma cholinesterases. Prolonged paralysis can occur in pseudocholinesterase deficiency, but this can be reversed by neostigmine (unlike paralysis due to SCh).

INTERACTIONS

1. *Thiopentone sod* and SCh solutions should not be mixed in the same syringe—react chemically.
2. *General anaesthetics* potentiate competitive blockers; ether in particular, followed by fluorinated hydrocarbons. Isofluorane, desflurane and sevoflurane potentiate to a greater extent than halothane. Nitrous oxide potentiates the least. Ketamine also intensifies nondepolarizing block. Fluorinated anaesthetics predispose to phase II blockade by SCh. Malignant hyperthermia produced by halothane and isoflurane in rare (genetically predisposed) individuals is more common in patients receiving SCh as well.
3. *Anticholinesterases* reverse the action of competitive blockers. Neostigmine 0.5–2 mg (30–50 µg/kg) i.v. is almost routinely used after pancuronium and other long/intermediate acting blockers to hasten recovery at the end of operation. Though neostigmine also reverses ganglionic blockade to some extent, hypotension and bronchospasm can occur due to muscarinic action of neostigmine; this can be prevented by prior atropinization (atropine or glycopyrrolate 5–10 µg/kg i.v.). Pretreatment with H_1 antihistamines reduces hypotension due to d-TC and others which release histamine.
4. *Antibiotics* Aminoglycoside antibiotics reduce ACh release from prejunctional nerve endings by competing with Ca^{2+}. They interfere with mobilization of ACh containing vesicles from a central location to near the terminal membrane, and have a weak stabilizing action on the postjunctional membrane. In clinically used doses, they do not by themselves produce muscle relaxation, but potentiate competitive blockers. The dose of competitive blocker should be reduced in patients receiving high doses of these antibiotics. Application of streptomycin powder locally at the end of bowel surgery has caused prolonged apnoea if a competitive blocker had been used during the operation. Tetracyclines (by chelating Ca^{2+}), polypeptide antibiotics, clindamycin and lincomycin also synergise with competitive blockers.
5. *Calcium channel blockers* Verapamil and others potentiate both competitive and depolarizing neuromuscular blockers.
6. *Diuretics* may produce hypokalemia which enhances competitive block.

7. *Diazepam*, *propranolol* and *quinidine* intensify competitive block, while high dose of corticosteroids reduces it.

Sugamadex This is a novel reversing agent developed for terminating the action of nondepolarizing muscle relaxants rocuronium and vecuronium. Sugamadex is a modified γ-cyclodextrin with high affinity for rocuronium and vecuronium; encapsulates one molecule of the blocker within its molecule forming an inactive chelate which is excreted in urine with a t½ of ~ 2 hours. As the plasma concentration of free rocuronium falls, it rapidly dissociates from the Nm receptor and neuromuscular transmission is restored. Thus, the mechanism of reversal by sugamadex is entirely different from that of the currently used reversing agents neostigmine and edrophonium. Sugamadex 2–4 mg/kg i.v. reverses rocuronium block within 3 min. in majority of patients. Its side effects are mild precordial pain, nausea, alteration of taste and rarely allergy. No cardiovascular effects have been noted.

TOXICITY

1. Respiratory paralysis and prolonged apnoea is the most important problem.
2. Flushing is common with d-TC (due to histamine release), can occasionally occur with atracurium and mivacurium, rare with others.
3. Fall in BP and cardiovascular collapse can occur, especially in hypovolemic patients. This is less likely with the newer drugs. Muscle relaxants should be used with great caution in patients with severe hepatic and renal disease.
4. Cardiac arrhythmias and even arrest have occurred, especially with SCh, particularly in digitalized patients. SCh releases K^+ from muscles. Intubating dose generally raises serum K^+ by 0.5 mEq/L, but dangerous hyperkalemia can occur, especially in patients with extensive burns and soft tissue injuries.
5. Precipitation of asthma by histamine releasing neuromuscular blockers.
6. Postoperative muscle soreness and myalgia may be complained after SCh.
7. Malignant hyperthermia can be triggered by SCh in patients anaesthetized with fluorinated anaesthetics.

USES

1. The most important use of neuromuscular blockers is as adjuvants to general anaesthesia; adequate muscle relaxation can be achieved at lighter planes. Many surgical procedures are performed more safely and rapidly by employing muscle relaxants. Muscle relaxants also reduce reflex muscle contraction in the region undergoing surgery, and assist maintenance of controlled ventilation during anaesthesia. They are particularly helpful in abdominal and thoracic surgery, intubation and endoscopies, orthopedic manipulations, etc.

Choice of the neuromuscular blocker depends on the nature and duration of the procedure, pharmacokinetics of the blocker and cardiovascular stability that it provides. Vecuronium and rocuronium are the most frequently selected nondepolarizing blockers.

SCh is employed for brief procedures, e.g. endotracheal intubation, laryngoscopy, bronchoscopy, esophagoscopy, reduction of fractures, dislocations, and to treat laryngospasm. For ocular surgery competitive blockers are preferred, because they paralyse extraocular muscles at doses which have little effect on larger muscles. Other factors which should be considered in selecting the relaxant are—onset of action, duration of blockade required, cardiovascular effects of the drug as well as patient's hepatic, renal and haemodynamic status.

Advantages of newer neuromuscular blockers over the older ones

- No or minimal ganglionic, cardiac or vascular effects.
- No or minimal histamine release.
- Many are short acting: easy reversal.
- Some are rapid acting: provide alternative to SCh without the attendant complications.

2. Assisted ventilation: Critically ill patients in intensive care units often need ventilatory support. This can be facilitated by continuous infusion of subanaesthetic doses of a competitive neuromuscular blocker which reduces the chest wall resistance to inflation. Vecuronium is most

commonly used, but after prolonged infusion it can cause blockade lasting 1–3 days due to accumulation of an active metabolite and/or development of neuropathy.

3. Convulsions and trauma from electroconvulsive therapy can be avoided by the use of muscle relaxants without decreasing the therapeutic benefit. SCh is most commonly used for this purpose. The short acting competitive blocker mivacurium is an alternative.

4. Severe cases of tetanus and status epilepticus, who are not controlled by diazepam or other drugs, may be paralysed by a neuromuscular blocker (repeated doses of a competitive blocker) and maintained on intermittent positive pressure respiration till the disease subsides.

DIRECTLY ACTING MUSCLE RELAXANTS

Dantrolene This muscle relaxant is chemically and pharmacologically entirely different from neuromuscular blockers; effect superficially resembles that of centrally acting muscle relaxants. Neuromuscular transmission or MAP are not affected, but muscle contraction is uncoupled from depolarization of the membrane. Dantrolene acts on the RyR1 (Ryanodine Receptor) calcium channels in the sarcoplasmic reticulum of skeletal muscles and prevents Ca^{2+} induced Ca^{2+} release through these channels. Intracellular release of Ca^{2+} needed for excitation-contraction coupling is interfered with. Fast contracting 'twitch' muscles are affected more than slow contracting 'antigravity' muscles. Since Ca^{2+} channels in the sarcoplasmic reticulum of cardiac and smooth muscles are of a different subtype (RyR2), these muscles are affected little by dantrolene.

Dantrolene is slowly but adequately absorbed from the g.i.t. It penetrates brain and produces some sedation, but has no selective effect on polysynaptic reflexes responsible for spasticity. It is metabolized in liver and excreted by kidney with a t½ of 8–12 hours.

Used orally dantrolene (25–100 mg QID) reduces spasticity in upper motor neurone disorders, hemiplegia, paraplegia, cerebral palsy and multiple sclerosis. However, it also reduces voluntary power; the resulting weakness considerably neutralizes the benefit and limits use to bedridden patients.

Used i.v. (1 mg/kg repeated as required) it is the drug of choice for malignant hyperthermia which is due to persistent release of Ca^{2+} from sarcoplasmic reticulum (induced by fluorinated anaesthetics and SCh in genetically susceptible individuals with abnormal RyR1, *see* p. 379). Reversal has also been obtained in neuroleptic malignant syndrome, though this reaction has a different pathogenesis.

Adverse effects Muscular weakness is the dose limiting side effect. Sedation, malaise, light headedness and other central effects occur, but are less pronounced than with centrally acting muscle relaxants. Troublesome diarrhoea is another problem. Long term use causes dose dependent serious liver toxicity in 0.1–0.5% patients. This has restricted its use in chronic disorders.

Quinine (*see* Ch. 59) It increases refractory period and decreases excitability of motor end plates. Thus, responses to repetitive nerve stimulation are reduced. It decreases muscle tone in myotonia congenita. Taken at bed time (200–300 mg) it may abolish nocturnal leg cramps in some patients.

CENTRALLY ACTING MUSCLE RELAXANTS

These are drugs which reduce skeletal muscle tone by a selective action in the cerebrospinal axis, without altering consciousness. They selectively depress spinal and supraspinal polysynaptic reflexes involved in the regulation of muscle tone without significantly affecting monosynaptically mediated stretch reflex. Polysynaptic pathways in the ascending reticular formation which are involved in the maintenance of wakefullness are also depressed, though to a lesser extent. All centrally acting muscle relaxants do have some sedative property. They have no effect

TABLE 25.3 Comparative features of centrally and peripherally acting muscle relaxants

Centrally acting	*Peripherally acting*
1. Decrease muscle tone without reducing voluntary power	Cause muscle paralysis, voluntary movements lost
2. Selectively inhibit polysynaptic reflexes in CNS	Block neuromuscular transmission
3. Cause some CNS depression	No effect on CNS
4. Given orally, sometimes parenterally	Practically always given i.v.
5. Used in chronic spastic conditions, acute muscle spasms, tetanus	Used for short-term purposes (surgical operations)

on neuromuscular transmission and on muscle fibres, but reduce decerebrate rigidity, upper motor neurone spasticity and hyperreflexia.

The prominent differences between peripherally and centrally acting muscle relaxants are listed in Table 25.3.

CLASSIFICATION

(i) *Mephenesin congeners* — Mephenesin, Carisoprodol, Chlorzoxazone, Chlormezanone, Methocarbamol.
(ii) *Benzodiazepines* — Diazepam and others.
(iii) *GABA mimetic* — Baclofen, Thiocolchicoside
(iv) *Central α_2 agonist* — Tizanidine

1. Mephenesin It was the first drug found to cause muscle relaxation in animals without producing unconsciousness and was called *internuncial neurone blocking agent* because its primary site of action is the spinal internuncial neurone which modulates reflexes maintaining muscle tone. It is not used clinically because orally it causes marked gastric irritation, and injected i.v., it causes thrombophlebitis, haemolysis and fall in BP. It has been included in counterirritant ointments *(MEDICREME, RELAXYL)* where its irritant rather than muscle relaxant property could be affording relief.

2. Carisoprodol It has a favourable muscle relaxant: sedative activity ratio with weak analgesic, antipyretic and anticholinergic properties. It is used in musculoskeletal disorders associated with muscle spasm.
CARISOMA 350 mg tab; one tab. TDS-QID, SOMAFLAM 175 mg + ibuprofen 400 mg tab.

3. Chlorzoxazone It is pharmacologically similar to mephenesin, but has a longer duration of action and is better tolerated orally.
FLEXON-MR 250 mg + ibuprofen 400 mg + paracetamol 325 mg tab; ULTRAZOX 250 mg + diclofenac 50 mg + paracetamol 325 mg tab; MOBIZOX 500 mg + diclofenac 50 mg + paracetamol 500 mg tab; PARAFON: 250 mg + paracetamol 300 mg tab, 1–2 tab TDS.

4. Chlormezanone It has antianxiety and hypnotic actions as well, and has been used for tension states associated with increased muscle tone.
DOLOBAK 100 mg + paracetamol 450 mg tab, 1–2 tab TDS.

5. Methocarbamol It is less sedative and longer acting than mephenesin. Orally it has been used in reflex muscle spasms and chronic neurological diseases. It can be injected i.v. without producing thrombophlebitis and haemolysis—used for orthopedic procedures and tetanus.
ROBINAX 0.5 g tab, 1 TDS: 100 mg/ml inj. for i.v. or i.m. use. ROBIFLAM 750 mg + ibuprofen 200 mg tab; NEUROMOL-MR 400 mg + paracetamol 500 mg tab.

Clinical efficacy of none of the above drugs as muscle relaxant is well established. Gastric irritation and sedation are the most important side effects.

6. Diazepam (*see* Ch. 29) It is the prototype of benzodiazepines (BZDs) which act in the brain on specific receptors enhancing GABAergic transmission. Muscle tone is reduced by supraspinal rather than spinal action; muscle relaxant: sedative activity ratio is low. No gastric irritation occurs and it is very well tolerated, though

sedation limits the dose which can be used for reducing muscle tone. It is particularly valuable in spinal injuries and tetanus. Combined with analgesics, it is popular for rheumatic disorders associated with muscle spasm.

Dose: 5 mg TDS orally, 10–40 mg i.v. (in tetanus).

7. Baclofen This analogue of the inhibitory transmitter GABA acts as a selective $GABA_B$ receptor agonist. The GABA receptors have been divided into:

$GABA_A$ receptor Intrinsic ion channel receptor which increases Cl^- conductance; blocked by bicuculline; facilitated by BZDs.

$GABA_B$ receptor G-protein coupled receptor; hyperpolarizes neurones by increasing K^+ conductance and altering Ca^{2+} flux; bicuculline insensitive, but blocked by saclofen.

Baclofen does not affect Cl^- conductance and its actions are not antagonized by bicuculline.

The primary site of action of baclofen is considered to be in the spinal cord where it depresses both polysynaptic and monosynaptic reflexes. As such, it does produce muscle weakness, but is less sedative than diazepam. Spasticity in many neurological disorders like multiple sclerosis, amyotropic lateral sclerosis (ALS), spinal injuries and flexor spasms is reduced, and baclofen is the preferred drug for symptomatic relief. However, it is relatively ineffective in stroke, cerebral palsy, rheumatic and traumatic muscle spasms and parkinsonism.

Baclofen is well absorbed orally and is primarily excreted unchanged in urine with a t½ of 3–4 hours.

Side effects are drowsiness, mental confusion, weakness and ataxia; serum transaminases may rise. Sudden withdrawal after chronic use may cause hallucinations, tachycardia and seizures.

Dose: 10 mg BD to 25 mg TDS.

LIORESAL, LIOFEN 10 mg, 25 mg tab.

8. Thiocolchicoside Chemically related to colchicine, this muscle relaxant is believed to act as a GABA mimetic and glycinergic drug. Combined with NSAIDs, it is being used for painful muscle spasms, such as torticolis, sprains, backache, etc. Side effects are gastric upset and photosensitivity reactions

Dose: 4 mg TDS-QID;

NUCOXIA-MR: Thiocolchicoside 4 mg + etoricoxib 60 mg tabs.

9. Tizanidine This clonidine congener is a central α_2 adrenergic agonist—inhibits release of excitatory amino acids in the spinal interneurones. It may facilitate the inhibitory transmitter glycine as well. Polysynaptic reflexes are inhibited resulting in decreased muscle tone and frequency of muscle spasms without reducing muscle strength. Efficacy similar to baclofen or diazepam has been noted in multiple sclerosis, spinal injury and stroke, with fewer side effects.

Tizanidine is absorbed orally, undergoes first pass metabolism and is excreted by the kidney; t½ 2–3 hours. It is indicated in spasticity due to neurological disorders and in painful muscle spasms of spinal origin. Side effects are dry-mouth, drowsiness, night-time insomnia and hallucinations. Dose-dependent elevation of liver enzymes occurs. Though no consistent effect on BP has been observed, it should be avoided in patients receiving antihypertensives, especially clonidine.

Dose: 2 mg TDS; max 24 mg/day.

SIRDALUD 2, 4, 6 mg tab, TIZAN 2, 4 mg tab; BRUFEN-MR, TIZAFEN 2 mg + ibuprofen 400 mg tab; TIZANAC 2 mg + diclofenac 50 mg tab, PROXIVON-MR 2 mg + nimesulide 100 mg cap.

Uses of centrally acting muscle relaxants

1. *Acute muscle spasms* Overstretching of a muscle, sprain, tearing of ligaments and tendons, dislocation, fibrositis, bursitis, rheumatic disorders, etc. cause painful spasm of muscles. The mephenesin-like and BZD muscle relaxants, combined with analgesics, are commonly used, but efficacy is not impressive.

2. *Torticollis, lumbago, backache, neuralgias* These are other conditions in which painful spasm of certain muscles is a prominent feature; respond in the same way as acute muscle spasms.

3. *Anxiety and tension* Increased tone of muscles often attends these states. Diazepam group

of drugs and chlormezanone benefit by their antianxiety as well as muscle relaxant actions.

4. *Spastic neurological diseases* Impairment of descending pathways in the cerebrospinal axis and withdrawal of inhibitory influence over the stretch reflex causes chronic increase in muscle tone or spasticity. Hemiplegia, paraplegia, spinal injuries, multiple sclerosis, ALS and cerebral palsy fall in this category. These conditions are benefited by baclofen, diazepam, tizanidine and dantrolene but not by mephenesin group of drugs. However, therapy of these disorders is far from satisfactory.

5. *Tetanus* Most commonly diazepam is infused i.v. and the dose is titrated by the response. Methocarbamol is an alternative.

6. *Electroconvulsive therapy* Diazepam decreases the intensity of convulsions resulting from ECT, without diminishing its therapeutic effect. Often SCh is used in addition for total suppression of the muscular component of ECT.

7. *Orthopedic manipulations* These procedures may be performed under the influence of diazepam or methocarbamol given i.v.

PROBLEM DIRECTED STUDY

25.1 A 30-year lady brought to the hospital emergency with 40% burn injury has to be operated under general anaesthesia.

(a) Which muscle relaxant should be preferred for tracheal intubation and a brief surgical procedure in this patient? Give reasons.

(see Appendix-1 for solution)