Drugs blocking neuro-muscular transmission

Drugs relaxing peripherally skeletal muscles

- The interaction of ACh with nicotinic cholinergic receptors, located in the postsynaptic membrane of the motor plate, opens the sodium channel, which is an integral part of the *N*-cholinergic receptor.
- The opening of the channel results in the inflow of Na^+ ions into the cells, relative to the concentration gradient. An increase in the concentration of Na^+ ions in the cytosol causes depolarization of the postsynaptic membrane and appearance of action potential. The biopotential of the plate spreads along the muscle fibre.
- The depolarization of the cell membrane of the muscle fibre leads to muscular contraction. The dissociation of the receptor-ACh complex blocks the sodium channel and releases ACh, which is decomposed to choline and acetic acid.

- The dislocation of sodium ions into the extracellular fluid and potassium ions into cells is caused by the sodium-potassium pump. It leads to repolarization of the motor plate and muscle relaxation.

- Drugs may influence neuro-muscular transmission. The blocking of neuro-muscular transmission is called a neuro-muscular block.

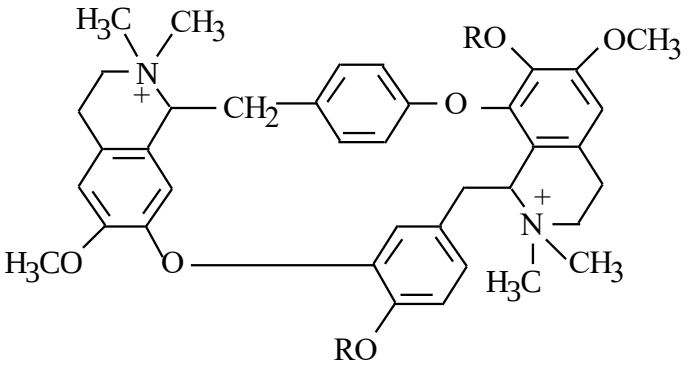
- There are two kinds of blocks:
- the nondepolarizing block and
- the depolarizing block.

Drugs with the nondepolarizing mechanism of action

- Drugs causing the nondepolarizing block compete with ACh. **They bind with the motor plate receptor and block the access of ACh to the motor plate**. ACh can not bind with receptors or increase the permeability of the cell membrane for Na^+ and K^+ ions, which cause depolarization and, after hydrolysis of ACh, plate repolarization. Inhibition of transmission and relaxation of skeletal muscles are observed.

- **AChE inhibitors are antagonists with competitive action**. The inhibition of ACh degradation involves an increase in the ACh concentration in the biophase and displacement of compounds creating the competitive block from the motor plate receptors. As a result the depolarization of the postsynaptic membrane is observed.

- (+)-Tubocurarine, an alkaloid isolated from *Chondodendron tomentosum* is a prototype of a drug with the nondepolarizing mechanism of action.

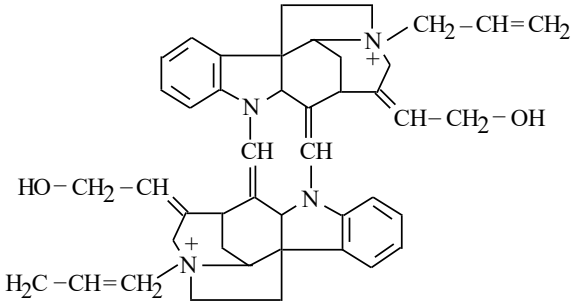


Tubocurarine, R = H;
TUBARINE

Dimethyltubocurarinium,
R = -CH_3

A molecule of tubocurarine contains two tetrahydroisoquinoline rings connected by two hydroxybenzyl groups. The nitrogen atoms in the tetrahydroisoquinoline group occur as quaternary ammonium salt and they are separated from each other by 10 atoms, which is equivalent to 1.5 nm. A tubocurarine molecule also contains two asymmetric carbon atoms. **Strong therapeutic action is shown only by the dextrorotatory form with the 1*R*,1'*S* configuration**.

- Alcuronium is a synthetic derivative of toxiferine – an alkaloid obtained from curare. Because alcuronium is not metabolized, it demonstrates long-term action.
- Alcuronium binds with plasma proteins. When the level of albumins is decreased, the same dose of alcuronium causes stronger action. The half-time of alcuronium is 3.3 h and it is prolonged to 16 h in anuria. 80-85% of the dose is eliminated in urine for 24 hours and the rest of the dose is secreted in bile for a long time.
- Alcuronium chloride is used in anesthesia during long surgical procedures to relax muscles.
- The muscle-relaxing action of D-tubocurarine is long. In large doses it also paralyses the autonomic ganglions and releases histamine.



Alcuronium, ALLOFERIN

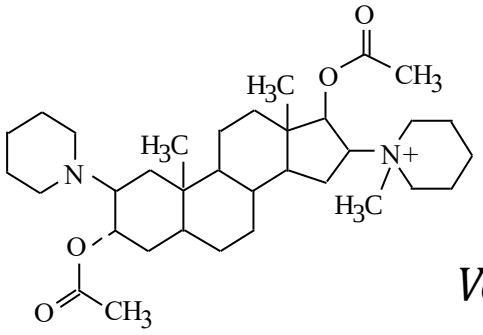
New derivatives with a less complicated structure and more selective action are used in therapy. They contain two quaternary ammonium units in:

- tetrahydroisoquinoline – (atracurium, doxacurium, mivacurium)
- piperidine – (vecuronium, pancuronium)
- piperazine (pipecuronium)

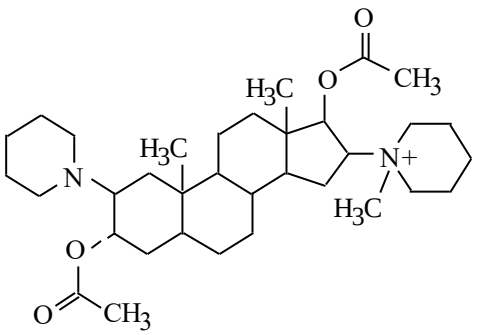
alkylated by methyl groups.

- Vecuronium has only one quaternary ammonium unit (piperidine). The second basic unit is piperidine. The ammonium units are bound with links. When the ammonium unit is built into an extended heterocyclic system, eg. tetrahydroisochinolin, its link may have a chain-like structure.

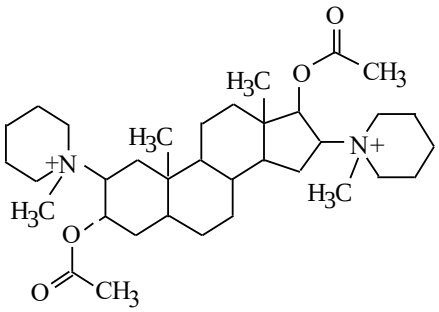
- When the ammonium unit contains smaller spacial units, eg. piperidine, piperazine, a cyclic molecule, such as 3,17-androstendiol (pancuronium, pipecuronium, vecuronium) is the link. Those drugs have various times of the start of action (1 – 3.5 min), the length of action (15-45 min) and the power of action. Strong muscle relaxing action, without releasing histamine, is shown by pancuronium and pipecuronium, 3,17-androstandiol derivatives. The action of ester derivatives is shorter because they easily hydrolyze.



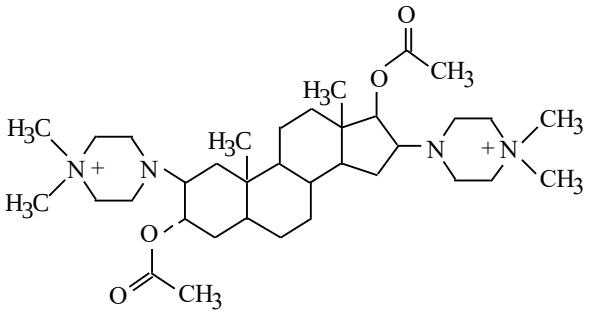
Vecuronium, NORCURON



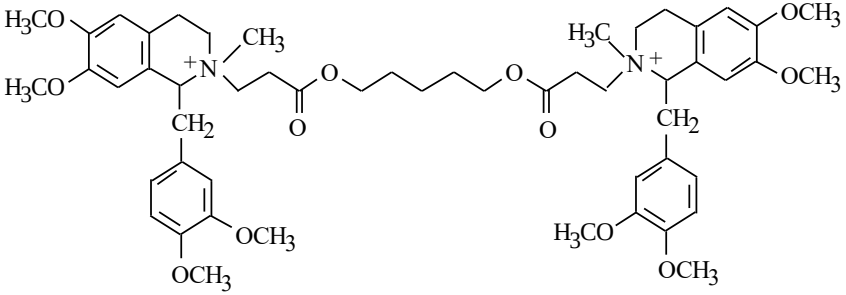
Vecuronium, NORCURON



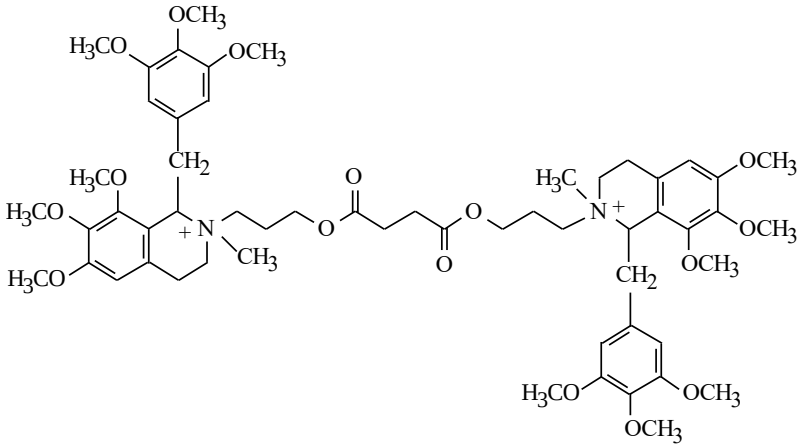
Pancuronium, PAVULON



Pipecuronium, ARDUAN



Atracurium, TRACRIUM



Doxacurium, NUROMAX

- The metabolism of drugs with the nondepolarizing mechanism of action is a result of the action of AChE. Only the metabolism of atracurium is a result of Hoffman elimination. Under physiological conditions it occurs at blood pH = 7.4 and at 37^0C.
- **Drugs with the nondepolarizing mechanism of action are used to relax striate muscles during surgical procedures in the abdominal cavity, chest and limbs. They are also auxiliary substances used to remove spastic spasms accompanying tetanus and strychnine poisoning.**
- Because they are not absorbed from the gastrointestinal tract, they are administered parenterally.
- **In higher doses they are a strong poison causing paralysis of skeletal muscles and stopping chest movement, which leads to death from suffocation.**

Drugs with the depolarizing mechanism of action

- The main structural parts of drugs paralysing neuro-muscular transmission are at least two quaternary ammonium groups situated at a specific distance from each other. Drugs causing the depolarizing block are substituted by methyl groups at nitrogen atoms and these ammonium groups are connected by a chain containing 10 atoms.

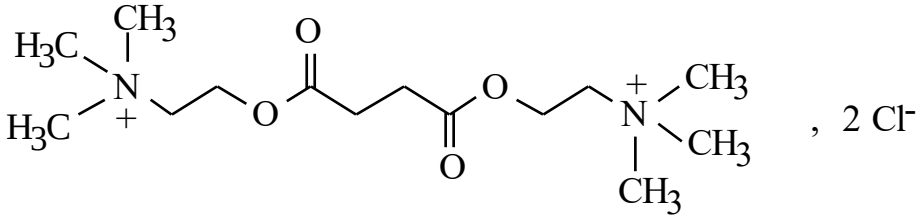
- It is possible to change the mechanism of action from competitive (depolarizing) to nondepolarizing. That can be achieved by increasing the distance between two ammonium groups, spatially extending the molecule between the ammonium groups or by replacing methyl groups with ethyl groups at nitrogen atoms.

- A reduced distance between two ammonium groups causes drugs to block the autonomic ganglions as a result of the polarizing mechanism of action (hexamethonium, azamethonium).

- **Drugs that cause the depolarizing block, similarly to ACh, depolarize the postsynaptic membrane, but the depolarizing time is longer because these drugs do not decompose as fast as ACh. Because of that repolarization is impossible and the transmission of next impulses is difficult. Under the influence of these drugs muscle tremor is initially observed and it is followed by muscle relaxation.**

- During the depolarizing block AChE inhibitors do not reduce the action of depolarizing drugs and they may even intensify this action. Drugs with the nondepolarizing mechanism of action are safer in therapy.
- When drugs causing the depolarizing block are used for a long time the patient may develop a reduced response to the same dose (tachyphylaxis – development of drug tolerance).
- The sensitivity of receptors to ACh is also decreased and the depolarizing block changes into the nondepolarizing block, which is removed by AChE inhibitors. This two-phase block, first depolarizing and next nondepolarizing, is called the double block.

- Suxamethonium is a drug with the depolarizing mechanism of action. It is a short-term action drug, which is caused by hydrolysis under the influence of AChE.
- When AChE inhibitors are used the action of suxamethonium is prolonged.
- When chlorsuccillin is administered intravenously the depolarization of the motor plates is observed after 30 s and this action lasts 3-5 min.
- Similarly to tubocurarine, chlorsuccillin is used in anesthesia during short surgical procedures and also to facilitate the endotracheal intubation at the beginning of anesthesia.



Suxamethonium chloride

ANECTINE, CHLORSUCCILLIN

Central action drugs relaxing skeletal muscles

- The spastic state of skeletal muscles is caused by disruption of transmission of motor impulses from the cerebral cortex to the anterior horns of the gray substance of the spinal cord along the pyramidal and extrapyramidal tracts.

- Impulses are transmitted by two types of neurons in the pyramidal tract
  - from the pyramidal cells of the cerebral cortex to the α anterior horns of the spinal cord and
  - from the α anterior horns of the spinal cord to the nerve-muscle endings of skeletal muscles.

- In the extrapyramidal tract impulses are transmitted by more types of neurons:
  - from the cerebral cortex or the cerebellum to the subcortical center and to the reticular structure
  - from the subcortical center to the γ cells of the anterior horns of the spinal cord
  - the cells of the anterior horns of the spinal cord to the nerve-muscle junctions of skeletal muscles.

- Spastic states occur when the transmission of motor impulses is disturbed at the following levels:
  - the first neuron in the pyramidal tract
  - the first and the second neurons in the extrapyramidal tract.

- Drugs inhibiting the spastic states of skeletal muscles act as follows:
  - at the level of the CNS (3-phenoxypropan-1,2-diol derivatives: chlorphenesin, mephenesine, methocarbamol)
  - at the levels of the CNS and the spinal cord (2-oxazolidonone derivatives: chlorzoxazone, mephenoxalone; propan-1,3-diol derivative – carisoprodol, propan-1-on derivative – tolperisone; 2,1,3-benzotiadiazol derivative – tizanidine; benzodiazepine derivative – tetrazepam)
  - at the level of the spinal cord (GABA derivatives – baclofen and idrocilamide)
  - directly on skeletal muscles (dantrolene).

- Flaccid paralysis with the atrophy of skeletal muscles occurs when a neuron in the section between the cerebral cortex cells and the endings of neuro-muscles is paralysed.
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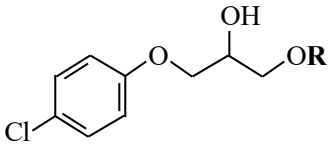
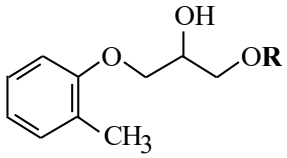
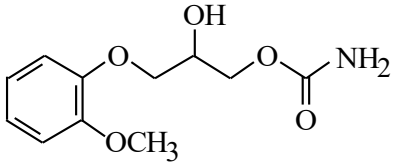
- When the cerebral trunk and the reticular structure at the level of the colliculus of the tectal lamina (tegmentum) are damaged, increased tension of muscles is observed.



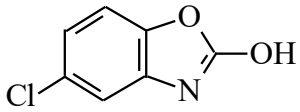
Chlorphenesine, R = H
Chlorphenesin carbamate, R = -O-CO-NH2; MAOLATE



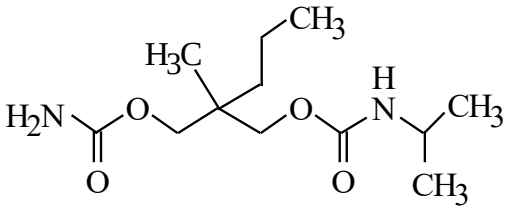
Mephenesine, R = H
Mephenesin carbamate, R = -O-CO-NH2; REOXYL



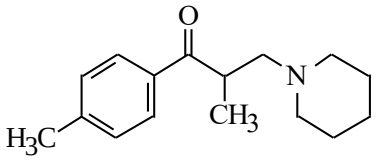
Methocarbamol, MESPEFAN, METHOCARBAMOL



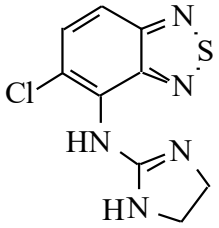
Chlorzoxazone, PARAFLEX



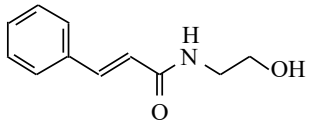
Carisoprodole, CARISOMA, SANOMA, SOMA,



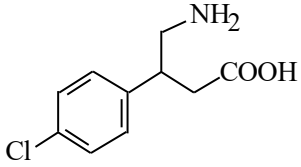
Tolperisone, MYDOCALM



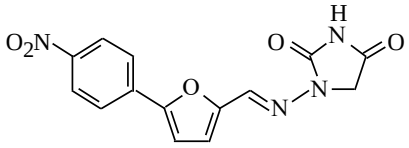
Tizanidine, SURDALUD



Idrocilamide, BROLITENE



Baclofen, BACLOFEN



Dantrolen, DANTROLEN

- The effect of the central action of the drugs presented above is similar to that of drugs acting on the motor plate, but the relaxing states of muscles last longer than after using curarizing drugs.

- Certain drugs, in addition to relaxing muscles, demonstrate other kind of action:
  - methocarbamol - antitussive and soothing
  - carisoprodol – local-anesthetic, weakly analgesic and soothing
  - tolperisone – weakly hypnotic
  - tetrazepam – sedative, anxiolytic and anticonvulsive
  - baclofen – sedative and hypnotic.

- These drugs are well absorbed from the gastrointestinal tract, so they may be administered orally. They are recommended in: chronic and acute spastic states of muscles appearing during certain rheumatic diseases, the pain syndromes of movement organs and in disc-radicular syndromes.

- The use of dantrolene is indicated to treat the spastic states of muscles caused by damage to the upper motor neuron and in the treatment and prevention of malignant hyperpyrexia (Chapter 14).