DRUGS ACTING ON THE CHOLINERGIC SYSTEM AND THE NEUROMUSCULAR BLOCKING DRUGS IV
(NICOTINIC ANTAGONISTS)
(PP XI)

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Drugs acting on the cholinergic system

Nicotinic antagonists

Objectives and intended learning outcomes:
The student should be able to

Describe the effects of nicotine and the ganglion-blocking drugs.

Classify neuromuscular blocking drugs, describe their mechanisms of action, report their clinical applications, state their adverse effects and interpret their interactions.
Nicotinic antagonists:

A-Ganglionic blocking drugs:

These agents act specifically on nicotinic receptors by blocking the ion channels in the ganglia both sympathetic and parasympathetic. Thus they block the entire output of the ANS at the nicotinic receptors. They have no effect on N-M junction. They were the 1st successful agents in the treatment of hypertension. However because of their adverse effect, they are rarely used nowadays. Examples of these drugs are hexamothanium, mecamylamine and trimetaphan.
Nicotine:

- present in tobacco smoke and is used in the form of chewing gum or transdermal patches by smokers to get rid of smoking and is still used in some insecticides. Depending on the dose nicotine:

- 1st stimulate the ganglia which is followed by blockade.

- The stimulatory effects are complex which include CNS stimulation ↑Bp, ↑HR (due to increase transmitter release from adrenergic nerve terminals and adrenal medulla), ↑peristalsis and secretion and ↑ADH release.

At higher doses Bp ↓ because of ganglionic blockade and the activity of the smooth muscles and secretion is blocked.
B- Neuromuscular blocking drugs:

These neuromuscular blockers are structural analogues of Ach they are either of

1- A non-depolarizing type: (act as antagonists) e.g. tubocurarine.

2- A depolarizing type (act as agonists) e.g. succinylcholine.

N-M blockers are clinically useful during surgery to produce complete muscle relaxation without the need to employ high anesthetic doses to achieve a comparable muscle relaxation.
CURARE Penetration Of The Dart
Absorption of toxin by skeletal muscles needed
Interruption of skeletal muscle contractions

Tubocurarine
Non-depolarizing type (competitive N-M blockers): (tubocurarine, pancuronium, gallamine, rocuronium, atracurium, mivacurium, vecuronium, doxacurium).

All of these drugs are given parenterally. They differ in their onset and duration of action. Rocuronium has the fastest onset of action),

whether they are metabolized by plasma choline esterase (e.g. mivacurium) or eliminated in bile (e.g. vecuronium)

or by the kidney (e.g. doxacurium, pancuronium, tubocurarine)

or eliminated by an independent mechanism (e.g. atracurium) which involves spontaneous breakdown called (hoffmann elimination).
Also these drugs differ in their autonomic effects and their ability to release histamine.

- *tubocurarine* blocks the ganglia and is the most likely of N-M blockers to cause histamine release.

Histamine release also occurs to a less extent with *atracurium* and *mivacurium*,

on the other hand *pancuronium* and *gallamine* block the cardiac muscarinic receptors causing tachycardia.
Mechanism of action of non-depolarizing agents:

These drugs compete with Ach and produce a competitive block at the end plate nicotinic receptors and thus prevent the depolarization of the muscle cell membrane causing flaccid paralysis.

The action of these drugs can be overcome by ↑ the concentration of Ach at the synaptic cleft e.g. by administration of ChE inhibitors (neostigmine or edrophonium)

some drugs in this group or when given in high doses may directly act to plug (close) the ion channels of the end plate, this leads to further weakening of N-M transmission and reduces the ability of ChE inhibitors to reverse the action of these drugs.
Tubocurarine

Acetylcholine

Nicotinic receptor at neuromuscular junction

Na⁺
small rapidly contracting muscles of the face and eye are the most susceptible to blockage and are paralyzed first followed by the muscles of the fingers then the limbs then neck and trunk muscles then the intercostals muscles and lastly the diaphragm.
Therapeutic uses:

these drugs are used mainly as surgical adjuvant to anesthesia for promoting skeletal muscle relaxation and for facilitating endo-trachial intubation.

Adverse effects:

1- Respiratory paralysis if mechanical ventilation is not provided.
2- Autonomic effect and histamine release depending on the drugs used (e.g. tubocurarine.)

Drug interactions:

Halogenated hydrocarbon anesthetics (halothane, Enflurane), aminoglycoside antibiotics (e.g. gentamycin, tobramycin), calcium channel blockers and some antiarrhythmic drugs (e.g. quinidine) increase the effect of N-M blockers. On the other hand ChE inhibitors antagonize their effect
Depolarizing agents:

**Succinylcholine (suxamethonium), decamethonium**

these depolarizing agents act like Ach on the nicotinic receptors of the motor end plate to depolarize the junction. But unlike Ach, succinylcholine (because is not rapidly hydrolyzed by ChE) remains attached to the receptor for a relatively longer time providing a constant stimulation of the receptor.

Succinyl choline therefore first causes the opening of Na – channel associated with nicotinic receptor which results in depolarization of the receptor (phase I) this leads to a transient twitching of the muscle (fasciculation).

The continued binding of the depolarizing agent render the receptor incapable of transmitting further impulses (desensitization) and results in flaccid paralysis (phase II) in which the membrane repolarizes but the receptor is desensitized to the effect of Ach. (a curare like effect).

*If a cholinesterase inhibitor is given phase I is augmented*
**PHASE I**
Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis.

**Nicotinic receptor at a neuromuscular junction**

**Succinylcholine**

**Na**

**PHASE II**
Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine.

**Succinylcholine**

**Na**

**Repolarized**
Therapeutic uses:

Because of its rapid onset and short duration of action (only few minutes if given as single dose) succinyl choline is useful for endotracheal intubation during induction of anesthesia and may be also used during ECT (electro-convulsive therapy).

Adverse effects:

- **Malignant hyperthermia** in genetically susceptible individual when succinyl choline is used in combination with Halothane (anesthetic), hyperpyrexia and muscle rigidity may occur, this is treated by rapidly cooling the body and by administration of Dantrolene which blocks the release of Ca from sarcoplasmic reticulum of the muscle cell thus reducing heat and decreasing muscle rigidity which is associated with hyperpyrexia.
Apnea: a genetically related deficiency of plasma ChE or the presence of atypical form of the enzyme can lead to prolonged apnea.

**Other adverse effects include:**
- post operative muscle pain,
- ↑ intragastric pressure which may promote emesis (vomiting),
- ↑ IOP
- ↑, hyperkalemia (especially in patients with burns).

Succinyl choline may cause stimulation of the autonomic ganglia and cardiac muscarinic receptor (bradycardia) and has a slight ability to release histamine.
Nicotinic antagonists include:

Ganglionic blocking agents;
they block the entire output of the ANS at the nicotinic receptors. They have no effect on the N-M junction

Neuro-muscular blocking drugs which are of types
Non depolarizing drugs
Depolarizing drugs

these drugs are used mainly as surgical adjuvant to anesthesia for promoting skeletal muscle relaxation and for facilitating endo-tracheal intubation.