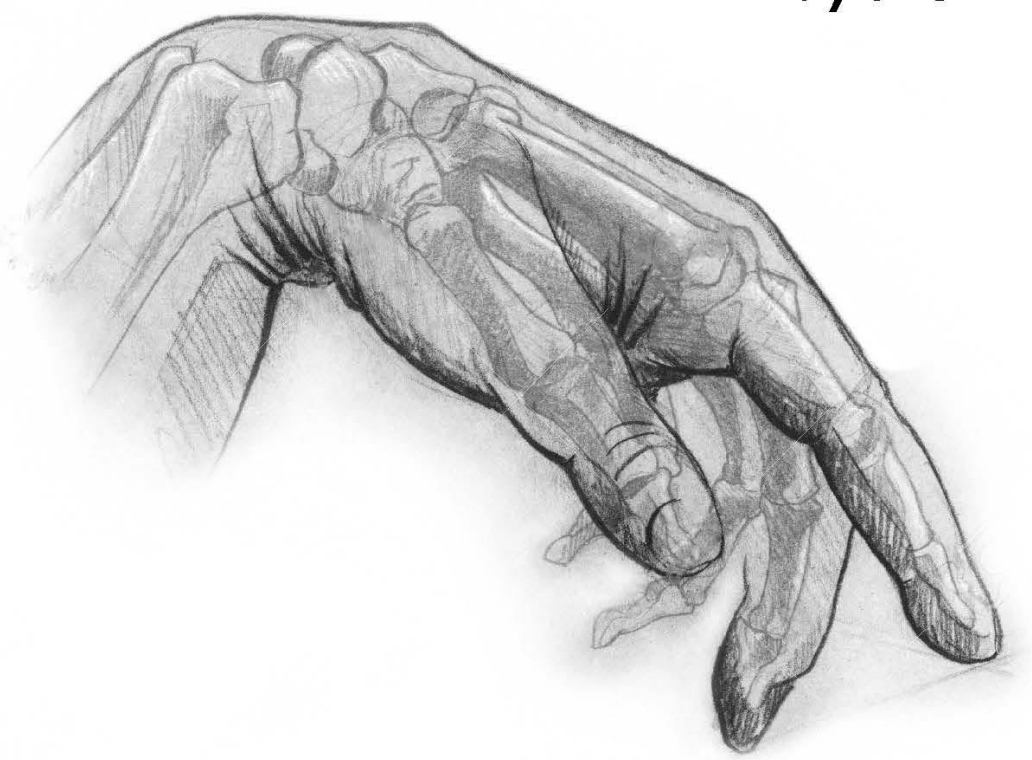
The

Musculoskeletal

System



Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number:	5
Subject:	Skeletal muscle relaxants
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Price: .....

This sheet will be talking about skeletal muscle relaxants. In order to understand their mechanism of action, here's a quick review of the neuromuscular junction:

When an impulse reaches the nerve terminal, it triggers the influx of calcium (Ca^{+2}) ions, which leads to the release of Acetylcholine by exocytosis. After that, it can bind to its receptors (nicotinic receptors) located at the membrane of the muscle, allowing the entry of Na^{+}, which in the end creates an action potential followed by muscle contraction . ACh is degraded by the enzyme Acetylcholinesterase .

Skeletal muscle relaxants:

Those are drugs that are going to interfere with the contraction of the muscle; normally, muscles require to contract to perform their function whether it was for bodily movements, digestion, respiration and etc…

So the question is, why is it needed to stop muscles from contracting?

In case of muscle spasms; continuous contraction of the muscle without relaxation. Also, in conjunction with general anesthesia, during surgeries that require intubation muscles must be relaxed.

There are two groups of skeletal muscle relaxants, and among these two, subgroups are found.

There is:

I. Neuromuscular blockers: drugs that work on the neuromuscular junction.
II. Spasmolytics (or the directly-acting): they work centrally on the brain, and some types work directly on the muscle itself.

Neuromuscular blockers:

These fall into two groups:

I. Depolarizing neuromuscular blockers: when bound to ACh receptors, they **persistently** depolarize the membrane of the muscle fiber, which makes it resistant to further stimulation by ACh.

II. Non-depolarizing neuromuscular blockers: ACh antagonists, they bind to the receptors and do not induce depolarization, inhibiting the contraction.

Non-depolarizing:

they are antagonist of nicotinic receptors , so they compete on binding site of ACH , the drug will bind receptor reversibly , so there will be competitive binding between the natural agonist and antagonist drug .

According to their chemical structures, there are two families:

i. Isoquinolines
ii. Steroid derivatives

NOTE: drug names in slide 7 are not required to be memorized. Although, certain things between these drugs will be distinguished.

Those drugs are used mainly during general anesthesia procedures.

The doctor mentioned the following:

Drugs that are eliminated through the kidneys tend to have longer duration of action than those eliminated through the bile or plasma ACh-esterase. Those with both hepatic and renal elimination have intermediate durations.

Most of these drugs (non-depolarizing) are excreted in the kidneys and metabolized by liver (except for Mivacurium that is metabolized by plasma

choline esterase, and Atracurium which is spontaneously broken down by a reaction called Hoffman elimination)

When they're metabolized in the liver, the resulting compound is a 3,17-hydroxyl(drug). This metabolite is not completely inactive, there is a 40-60% activity left.

Thus, when a patient is given the drug for long period of time (i.e. ICU patients), the partially active drug will still exert effect, and lead to longer paralysis of the muscle (which is reversible).
Meanwhile, if it is given only for a surgical procedure, there will be no accumulation and the metabolite is not able to paralyze the muscle.

If a look is taken at the structure of the neuromuscular blockers generally, a resemblance to ACh is noticed. Both Succinylcholine (depolarizing) and Pancuronuium (non-depolarizing) have two Acetylcholines bound together within their structures.
This resemblance is what makes them capable of binding to ACh's receptors.

Also, it is noticeable that the chemical structure of the neuromuscular blockers is highly polar; the presence of one or two quaternary Nitrogens, making them poorly lipid soluble.
Having said that, it is concluded that they do not reach the CNS, are not well-absorbed orally and so, must be given parentally as IV injections.

First discovery of neuromuscular blockers:

When early Europeans went to North America, they noticed how the natives would shoot arrows at animals, that left them paralyzed and easy to hunt. Later on, turned out that the native Americans had covered the tips of the arrows with Curare extract, a muscle relaxant.

Because this compound is not well absorbed orally, ingestion of the injected animal meat did not affect the natives.

The chemical structures of drugs are not required, but the pharmacokinetics are. Refer to slides 13 and 14, do not memorize the exact numbers of the duration of action, rather, try to link the route of elimination with the duration.

- On a side note, Atracurium's metabolite is called Laudanicine, which is toxic in high concentrations, and has been associated with seizures.

Depolarizing neuromuscular blockers:

An example of which is Succinylcholine. It is a polar drug that is administered parentally and metabolized by cholinesterase, thus, has a short duration of action.

Only a small percentage of it reaches the neuromuscular junction, and diffuses away into the extracellular fluid.

It is important to mention that cholinesterase exhibits genetic polymorphism among individuals, and the degree of its activity varies, therefore, a test (called the Dibucaine test or number) is performed to determine the activity.

Dibucaine, a compound used as a local anesthetic, is an inhibitor of the enzyme. And so, according to the amount of inhibition, the degree of enzyme function is determined.

Genotyping is also possible, but this test is less expensive and more available, although it is less accurate.

If toxicity occurs using a depolarizing blocker, an antidote is used. Antidotes are acetylcholines esterase inhibitors; inhibition of the enzyme would increase the concentration of ACh that can competitively replace the depolarizing blocker at the receptors.
Neostigmine is an example of antidotes.

Sarine gas, toxicity by which occurred frequently during wars, causes depolarizing blockade of the muscle; continuous contraction that would leave

the muscle desensitized and unable to contract any further.

Insects are killed similarly using pesticides.

Mechanism of action:

They initially bind to the receptors causing depolarization through the opening of Na^+ channels, and they can also enter the channel further prolonging the ion conductance. During that, the muscle remains depolarized and unresponsive (Phase 1 block).

After continuous exposure, the depolarization decreases and the membrane repolarizes, but it cannot be depolarized again because now it is desensitized (Phase 2 block).

As mentioned before, all that can be terminated using ACh-esterase inhibitors.

For drugs with short duration of action such as, Mivacurium and Succinylcholine, longer duration of action can be accomplished through continuous administration. Also, for patients that undergo intubation for a long period of time, muscle relaxants that are excreted through the kidneys are used.

Drug-drug interactions associated with neuromuscular blockers:

General anesthesia drugs like Isoflurane affect their action, Certain antibiotics like Aminoglycosides, as well as some calcium channel blockers can interfere with their action, increasing the concentrations of these muscle relaxants.

These interferences have both sympathetic and parasympathetic manifestations on the heart, or even through histamine receptors.

They can cause hypotension (antihistamines are used in this case), and hyperkalemia; they interfere with potassium channels leading to increased

concentrations in blood stream, putting patients at risk of developing cardiac arrhythmias.

Some of these drugs, specially Succinylcholine, can cause a condition called Malignant Hyperthermia, which is usually associated with the administration of general anesthetics.

In malignant hyperthermia, there is excess release of Ca^{+2} from the endoplasmic reticulum that is mediated by ryanodine receptors. This results in excessive muscle contraction and heat production that can be fatal (seizures may be associated, plus lactic acidosis).

Dantrolene, a spasmolytic, is a drug that inhibits these receptors and is therefore used to treat this condition.

Spasmolytics:

Muscular relaxants that are used in case of chronic neurologic disease such as, multiple sclerosis. Or, in case of acute injuries such as, acute spinal cord injuries and muscle inflammation.

Diazepam (Valium):

A spasmolytic that works centrally through the activation of GABA receptors, that inhibits muscle tone. GABA activation can cause sedation as well.(sedation considered to be a side effect).

In certain procedures, it is not needed to anesthetize the patient fully (ex: wisdom tooth extraction), it is only required for the patient to be calm, and the muscles relaxed. These muscle relaxants are used in this case.

Baclofen:

It works on GABA receptors as well, and inhibits muscle contraction. Good thing about this drug is that, it does not cause sedation. Or more accurately, sedation occurs for a short time initially, after that it is tolerated and diminished.

Drug can be given intrathecally, so for patients with chronic conditions, it is stored intrathecally and continuously released.

It is used in the recovery of alcoholism and can be used for stopping migraine.

Tizanidine is a spasmolytic related to **Clonidine**, both have spasmolytic activity by affecting autonomic nervous system.

Gabapentin, an anticonvulsant used for seizures. And because people suffering from seizures have similar initiations of action potentials, this drug can be used for the inhibition of muscle spasms as a spasmolytic agent.

Dantrolene (already mentioned), works directly on the muscle itself and inhibits its contraction.

Botulinum toxin:

Produced by bacteria, it inhibits the release of ACh and causes muscle paralysis. It is used cosmetically for the removal of wrinkles, and is also used for systemic conditions such as cerebral palsy.

Food poising by this toxin is likely to occur within 12-36 hours after ingestion.

** Doctor said that the clinical details mentioned in the slides are not important. If you get confused reading the sheet, refer to the slides they are clear.

Also, we are covering chapter 27 from Katzung's.

May Allah grant you success, good luck.