MSS

Sheet no. 3

Pharmacology

Writer: Ahmad T Qatawneh
Corrector: Haitham Alsaifi
Doctor: Alia Shatanawi

- ## Keratolytic and destructive agents (recap):
    1- **Salicylic acid** (discussed in previous sheet)
    2- **Propylene Glycole** (discussed in previous sheet)
    3- **Urea** (discussed in previous sheet)
    4- **Podophyllum Resin and Podofilox** (Just know the name)
    5- **Fluorouracil**
    6- **NSAIDS**
    7- **Aminolaevulinic acid**

Fluorouracil

- An antimetabolite that has a structure resembling that of **Uracil** and therefore it can inhibit the enzyme **Thymidylate synthetase,** thus interferes with DNA and may be RNA synthesis.
- Used for the treatment of **Actinic keratosis (**Precancerous lesion).

Nonsteroidal anti-inflammatory Drugs

- 3% gel topical formulation of **Diclofenac**
- NSAIDS can also be used systemically by pills or injections

Aminolevulinic acid

- Used in **Actinic keratosis** in the form of 20% topical application.
- However, Topical application combined with exposure to light produces **ROS (Cytotoxic superoxide and hydroxyl radicals)** leading to a case of **Light eruption of the skin.**

- ## Antipruritic Agents
    - **Pruritis** is medical condition characterized by itchiness of the skin as a part of an inflammatory response in which mast cells (for example) secrete **Histamine**.
    - The difference between first generation and second-generation antihistamine drugs is that 1st-gen can pass BBB and therefore cause the drowsiness symptoms, whereas 2nd-gen drugs cannot pass the BBB and therefore cannot cause drowsiness.
    - 2 drugs are used to treat this condition:

1- Doxepine (first generation antihistamine):

- Potent H1 (Present in CNS) , H2 (Present in the stomach) receptor antagonist.
- **H1-antagonism side effects:** responsible for the drowsiness and anticholinergic effects.
- **H2-antagonism:** used for treatment of stomach peptic ulcers.

2- Pramoxine

- Topical local anesthetic agent and therefore alleviates the sensation of itchiness.

• Trichogenic (Hair growth) and Antitrichogenic (Hair loss) agents

1- Minoxidil (Rogaine) Trichogenic

- **Originally designed as an antihypertensive agent** (By activating certain K+-channels leading to hyperpolarization followed by the closure of Na+ channels and therefore no calcium release in these smooth vascular muscle cells leading to relaxation and dilation of blood vessels and hence decrease in blood pressure. **Later, was found to have a beneficial side effect in treating Androgenic alopecia associated hair loss**.
- Effective in the treatment of male pattern boldness usually associated with patients with **Androgenic Alopecia** (a genetic condition leading to hormonal loss of hair)
- Also effective in reversing the progressive miniaturization (تراجع خط الشعر) of terminal scalp hairs also associated with **Androgenic alopecia.**
- Vertex balding is more responsive than frontal balding.

2- Finasteride (Propecia) Trichogenic (Promotes hair growth)

- **5 alpha-Reductase inhibitor** which blocks the conversion of testosterone to dihydrotestosterone thereby affecting the growth of hair. (Dihydrotestosterone is one of the androgens associated with hair loss in **androgenic alopecia**).
- Given orally by tablets.
- Side-effects: decreased libido(Sexual drive), ejaculation disorders, and erectile dysfunction.

3- Eflornithine (Anti-Trichogenic)

- Acts as an **irreversible inhibitor of ornithine decarboxylase** therefore inhibiting polyamine synthesis which are important in cell division and hair growth, ultimately leading to decreased hair growth.
- Effective in reducing facial hair growth in 30% of women when used for 6 months.

• Drugs for leishmania

- **Leishmaniasis is a parasitic disease caused by leishmania species**:
  1- **L.Tropica**: Cutaneous leishmaniasis or Oriental sore.
  2- **L.Brazeliensis**: Mucocutaneous Leishmaniasis.
  3- **L.Donovani:** Visceral leishmaniasis (Most severe form)

Drugs used to treat leishmaniasis:

1- Sodium Stibogluconate

- Best drug for all types of leishmaniasis. Belongs to the family of drugs known as **Pentavalent antimonial**. (It has 2 mechanism)
- Binds to the SH groups of the pathogen proteins causing their unfolding and ultimately killing the pathogen (**1st mechanism**)
- **The 2nd mechanism** is by inhibiting the enzyme **Phosphofructokinase** (Necessary for the metabolism of the pathogen).
- Typical preparations contain 30% to 34% pentavalent antimony by weight as well as m-chlorocresol added as a preservative.
- **Administration: Local, IM or slow IV**, (can be irritant when given in injection form). **Given for 20-28 days.**
- Although considered Drug of choice for all forms of leishmaniasis. **Resistance is increasing**, especially in India (which is why is it given along with other drugs in certain cases)
- **Side-effects: Cough, V(Vomiting), D(diarrhea), arthralgia, ECG changes, Rash, Pruritis**.

2- Amphotericin

- An anti-fungal agent that is toxic, difficult to use. Used In areas where leishmania is resistant as an alternative for the treatment of **visceral leishmaniasis**.

3- Miltefosine

- For visceral leishmaniasis
- Given orally, for 28 days.
- Causes V & D, hepatotoxicity, nephrotoxicity, and it is teratogenic.

4- Pentamidine

- Inhibitor of **Dihydrofolate reductase** and DNA replication**.**
- Given IM or IV injection and Inhalation.
- Binds avidly to tissues, not the CNS.
- It can be used against different organisms including:
  1- **Leishmaniasis**: Alternative to Na stibogluconate
  2- **Pneumocystis jiroveci**: Treatment and prophylaxis of patients who cannot tolerate or fail other drugs.
  3- **Trypanosomiasis**: For early hemolymphatic stage.
- **Adverse Effects**: 1. Rapid Infusion: Hypotension which leads to two other symptoms compensatory tachycardia and dizziness.
  2. Pain at the injection site.
  3. Others: Pancreatic, Renal, and Hepatic toxicity

• Antilepromatous Drugs

1- Dapsone and Sulphones

- Related to sulphonamides which are inhibitors of folate synthesis. However, Resistance develops rapidly and therefore they are usually combined with **Rifampin** (Anti-TB medications) and **clofazimine.**
- Also used for Pn. Jeroveci in AIDS patients.
- **Well absorbed and distributed**.
- **Retained in the skin** (Convenient as leprosy usually involve the skin), muscle, liver and kidney.
- **Side effects**:
  1- Hemolysis, particularly in **G-6-PD deficiency**.
  2- **GIT intolerance** (A triad of Nausea, Vomiting and diarrhea)
  3- Fever, Pruritus, Rashes.
  4- **Erythema Nodosum Leprosum** (In small number of patients) which is a painful inflammatory complication of leprosy characterized by fever rashes and general malaise. This inflammatory condition is suppressed by **Steroids or Thalidomide.**

❖ **Note: Thalidomide** was previously used to treat nausea of pregnancy until it was found to be teratogenic leading to missing limbs in children. Lately, it was shown that this drug is beneficial in treating Multiple Myeloma (MM).

2- Rifampin: – Discussed with antituberculosis drugs.

3- Clofazimine:

- Binds to DNA.
- Stored widely in Reticuloendothelial system (RES) and skin.
- Released slowly from storage sites, half-life, t1/2 = 2 months.
- **Given for sulphone- resistant or intolerant cases**.
- Causes **skin discoloration (red brown to black) and GIT intolerance**.

The end of the skin part

Skeletal muscle Relaxants

There are 3 types of skeletal muscle relaxants:

1- **Neuromuscular Blockers:**

- Nondepolarizing Drugs (Competitive antagonists)
- Depolarizing Drugs (Non-competitive Agonists)

2- **Spasmolytics**

3- **Directly Acting Drug**

Neuromuscular Blockers

➢ **Chemistry**:

- One or two quaternary nitrogens'', i.e., poorly lipid soluble or highly polar compounds.
- Double acetylcholine molecules linked: either End to end (**Succinylcholine**, a **depolarizing drug**) or concealed, bulky semi- rigid ring systems (**Tubocurarine**, a **Nondepolarizing drug**)

➢ **Pharmacokinetics**:

- Must be given parenterally whether Depolarizing or Non-Depolarizing.
- Nondepolarizing Drugs:

1. Excreted in the kidney (short half-life) or metabolized by the liver (longer half-life).
2. **Mivacurium** is metabolized by cholinesterase's (Thus a short half-life).
3. **Atracurium** is spontaneously broken down by interacting with water (**HOFMAN ELIMINATION**) (Thus a short half-life)

Note: Classifying these drugs as short – intermediate – long half-life drugs is clinically relevant to decide which drug is best for our clinical scenario (Different durations of surgeries for example require different types of relaxants).

- Depolarizing Drugs:
  1- Extremely short duration (5-10 minutes.)
  2- Metabolized by cholinesterase's in the plasma and liver.
  3- Only a small percentage reaches the neuromuscular junction, where it diffuses away into the extracellular fluid.
  4- Some patients have a genetically abnormal variant of plasma cholinesterase and for that reason, we refer to Dibucaine Number which is a measure of the ability of a patient to metabolize succinylcholine.

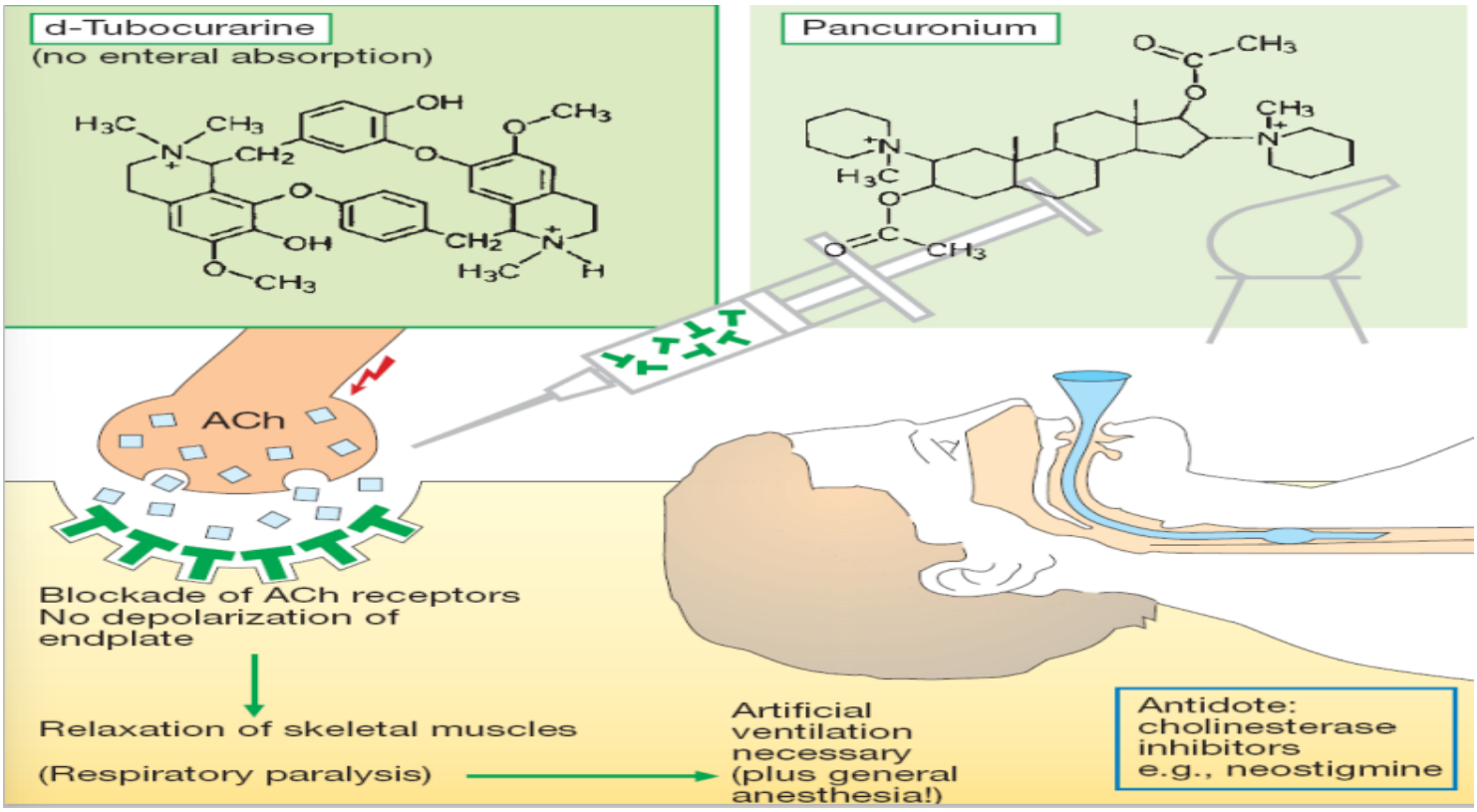
Table 27–1. Some properties of neuromuscular blocking drugs.

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	> 35	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	> 35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	> 35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6
Depolarizing agent				
Succinylcholine	Plasma ChE[2] (100%)	>100	< 8	0.4

[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.
[2]Butyrylcholinesterase (pseudocholinesterase).

- **Mechanism of action:**
- Nondepolarizing Drugs: the most famous one (**d-Tubocurarine**)

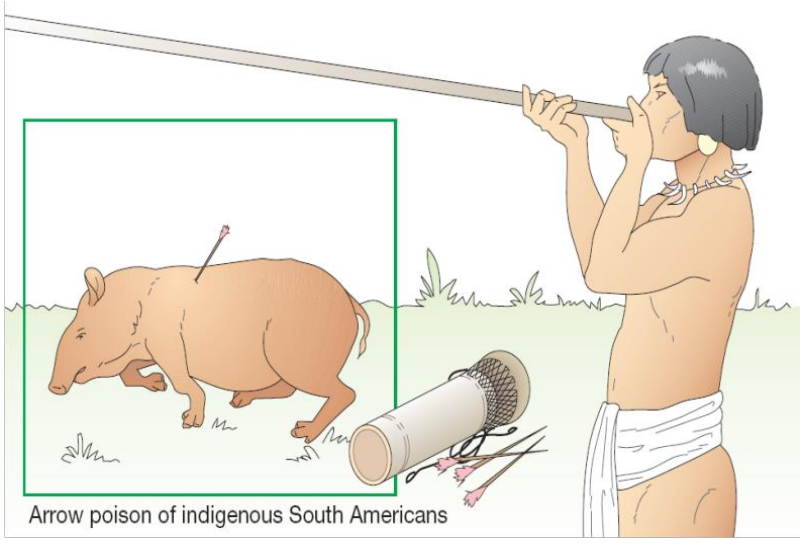
1- Compete with acetylcholine at the nicotinic receptor sites at the NMJ.
2- In high doses, can enter the pore of the ion channel to cause a more intense blockade known as (**Non-depolarizing Neuromuscular blockade**)
3- Can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending.



❖ Regarding the previous Figure:

- **D-Tubocurarine** is the prototype (not used anymore) for other similar non-depolarizing drugs with better pharmacodynamic properties including (**Pancuranium**).
- It functions as an **antagonist (Blocker) for Nicotinic Ach receptors** present at the neuromuscular junction leading to relaxation of these muscles and therefore **respiratory paralysis** (This is why patients in surgeries are artificially ventilated as well as given a general anesthesia).
- **The Antidots** for D-Tubocurarine are **Cholinesterase inhibitors** (Ex: **Neostigmine**) which inhibit AchE and therefore increasing the concentration of the endogenous ligand Ach.

❖ Fun fact: tubocurarine was used by the native Americans to induce Paralysis In the animals they hunt so that they can catch them.


Arrow poison of indigenous South Americans

The end