**5-Centrally acting muscle relaxants**

Muscle relaxants are a drug which affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms and pain.

**Types of Muscle Relaxants**

1. **Neuromuscular Blockers (Peripherally acting)**
   They act by interfering with transmission at the neuromuscular end plate and have no central nervous system activity.

2. **Centrally acting" muscle relaxants (Spasmolytics)**
   They are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions.

3. **Direct acting skeletal muscle relaxants**
   e.g. Dantrolene

**Centrally acting" muscle relaxants (Spasmolytics)**

1. **Baclofen (Lioresal)**
   **Mode of action**
   It is substituted GABAB analogue.
   It causes hyperpolarization by increased K⁺ conductance in the postsynaptic membrane, reducing calcium influx in the presynaptic terminal.
   It reduces excitatory transmitter in brain as well as spinal cord
   (-)-Baclofen is the active isomer
   Less sedation than BZDs and it is now used in chronic conditions

2. **Tizanidine (Sirdalud)**
   a₂ adrenergic receptor agonist (Congener of clonidine)
   Presynaptic inhibition of motor neurons
   1/10-1/50th potency as clonidine in lowering blood pressure
   **Side Effects:** Drowsiness, hypotension, dry mouth

3. **Diazepam**

4. **Chlorzoxazone (Myolgin)**
   It acts on the spinal cord by depressing reflexes.
Chlorzoxazone reversibly increased \( \text{Ca}(2+) \)-activated \( K(+) \) current \((I(K(Ca)))\) (Calcium-activated potassium channel)

N.B. Paracetamol is used as adjuvant therapy to relief pain

2-Direct acting skeletal muscle relaxants

\textit{Dantrolene}

\textbf{Mode of action}
It interferes with the release of calcium from its stores in skeletal muscles (sarcoplasmic reticulum). It inhibits excitation-contraction coupling in the muscle fiber.

N.B. Paracetamol is used as adjuvant therapy to relief pain

6-\textbf{General Anesthetics}

Drugs that are given to the patient that have different effects with the overall aim of ensuring unconsciousness, amnesia and analgesia. General anesthetics cause descending depression of the central nervous system; starting with the cerebral cortex, the basal ganglia, the cerebellum and finally the spinal cord.

\textbf{General anesthesia occurs in four distinct stages:}

\textbf{1- Stage I (Analgesia; induction):}
Start from beginning of anesthetic administration and last up to loss of consciousness, feels a dream like state, reflexes and respiration remain normal Twilight Sleep.

\textbf{2- Stage II (Delerium; Excitement):}
From loss of consciousness to beginning of irregular respiration. Apparent excitement is seen. Muscle tone increases. Jaws are tightly closed. Heart rate and blood pressure may rise. Best to get through phase II as quickly as possible.

\textbf{Stage III: Surgical anesthesia}
Extends from onset of irregular respiration to cessation of spontaneous breathing. This has been divided into 4 planes

- Plane 1: This plane ends when eyes become fixed.
- Plane 2: Loss of corneal and laryngeal reflexes.
Plane 3: Pupil start dilating and light reflexes.
Plane 4: Dilated pupil, decrease muscle tone, BP

*This is the stage in which most of surgeries are performed.* falls.

**Stage IV:** Medullary paralysis:
This stage results from *overdose toxicity* that leads to depression of vital centers of medulla it may involve respiratory failure and collapse of the vital motor functions and therefore, lead to death.

- **To achieve safe anesthesia: short stage 1, rapid stage 2 and NO stage 4 are required.**

**Adjuvant to General anesthesia or (Combined Anesthesia)**
This practice fulfills many of purposes such as:

1-Controlling pain is achieved by using strong *narcotic analgesics* such as *morphine* and *fentanyl*. The latter is used to induce unconsciousness thereby reducing the dose of the anesthetic used.

2-Reducing anxiety, *benzodiazepines sedatives* are used such as *diazepam*, *lorazepam* and *midazolam*.

3-Inhibiting respiratory secretion & salivation and to prevent hypotension, *anti-cholinergics* such as *scopolamine* and *atropine* are used.

4-Prevention of nausea and vomiting by using *antiemetics* such as *promethazine* and *chlorpromazine*.

5-Relaxing muscles for optimum surgical working by using *skeletal muscle relaxants*.

**Mechanism of Action of General Anesthetics**

- Inhibition of *NMDA and glutamate receptors controlled channels* e.g. Halothane, Halogenate ether, Ketamine
- By activation of inhibitory *GABA receptor controlled channels* propofol, midazolam, thiopental

**Ideal Inhalation anesthetic should be:**

- Non inflammable,
- Potent, having wide margin of safety and low toxicity,
- Not affecting myocardial functions or respiration at anesthetic doses, with good muscle relaxation,
- With uncomplicated/pleasant induction and emergence,
1. Inexpensive and easy to administer,
2. Chemically & metabolically stable.

**1-Inhalation Anesthetics (Pulmonary)**

A. **Volatile Halogenated Hydrocarbons**

**Halothane (Fluothane)**

2-Bromo-2-chloro-1,1,1-trifluoro ethane

Non-flammable volatile liquid.

-Packaged in amber bottles containing *0.01% thymol as stabilizer* as it undergoes spontaneous oxidation to HCl+ HBr+ Br⁻+ Cl⁻+ COCl₂ (phosgene).

-High potency, volatility and chemical stability due to fluorine.

**Metabolism of Halothane:**

Mostly eliminated intact but about 20% is metabolized as follows:

\[
\text{CF}_3\text{CHBrCl} \rightarrow [\text{CF}_3\text{CBrClOH}] \rightarrow \rightarrow \rightarrow \text{CF}_3\text{COCl} + \text{HBr}
\]

Carbinol \[\text{trifluoro-acetylchloride} \rightarrow \rightarrow \rightarrow \text{CF}_3\text{COOH} + \text{HCl}\]

**Side effects: (narrow margin of safety)**

Falling of cardiac output, contractile force & blood pressure during its administration.

Increased possibility of arrhythmias.

It has a negative effect on liver function. On repeated use cause **hepatotoxicity** due to the metabolites produced (immunoreactive response is suggested).

<table>
<thead>
<tr>
<th>Desflurane</th>
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| \[
\text{F}_3\text{C} = \text{O} = \text{F}
\] |
| 1,2,2,2-Tetrafluroethyl- difluoro methyl ether |
| Non-flammable, liquid pungent odor. |
| Replacement of Cl with F, decrease blood/ gas P.C→ twice rapid induction and recovery than isoflurane *(for out-patient surgical procedures)* |

**Metabolism of Desflurane**

C-F is a stable bond so only **0.02%** of drug is metabolized to F⁻ ions and TFA (trifluoroacetic acid) thus the drug is not associated with hepato or neprotoxicity
## 2-I.V. Anesthetics

<table>
<thead>
<tr>
<th>1-Propofol (Diprivan®)</th>
<th>2-Ketamine (Ketalar®)</th>
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<tbody>
<tr>
<td><img src="image1" alt="Propofol Structure" /></td>
<td><img src="image2" alt="Ketamine Structure" /></td>
</tr>
<tr>
<td>-Activates inhibitory GABA in CNS</td>
<td>-Blocks NMDA controlled channels</td>
</tr>
<tr>
<td>-Rapid onset, hypnosis within 1 min, Short acting (5 min)</td>
<td>Very potent, moderately rapid acting, short duration (10-25 min)</td>
</tr>
<tr>
<td>-Maintenance with volatile anesthetics</td>
<td>-<strong>Dissociative or cataleptic analgesia</strong></td>
</tr>
<tr>
<td>-More effective than thiopental</td>
<td></td>
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</tbody>
</table>

Used in outpatient surgical procedure (rapid recovery) & patients suffering from respiratory depression

**Drawbacks:** transient hypotension (Caution in old patients)

Can be used as a sole agent in minor surgical procedure that does NOT require muscle relaxation, or it is used to induce anesthesia which is maintained by inhalation anesthesia

Patients older than 16 years → (27%) post operative adverse psychological experiences (i.e., producing wild dreams and hallucination during emergence may last for 24 hr (So, **ONLY for children & infants**)

### Synthesis of Propofol:

![Propofol Synthesis](image3)

**Ultra-short acting barbiturates**

3-Thiopental

Sodium-5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate.
High lipophilicity is due to Sulfur and the long side chain. It crosses BBB extremely rapidly and produces unconsciousness in 20-30 seconds then it undergoes partitioning from brain to body fat.

**Benzodiazepines**

*4-Midazolam maleate*

-used for induction of anesthesia & pre-operative sedation

Short duration (*due to metabolic hydroxylation then conjugation*)

N.B BDZ alone cannot produce surgical anesthesia, only used for induction.

---

**Local Anesthetics**

Local anesthetic is a drug that causes reversible local anesthesia and a loss of nociception. When it is used on specific nerve pathways (nerve block), effects such as analgesia (loss of pain sensation) and paralysis (loss of muscle power) can be achieved.

It reversibly blocks impulse conduction along nerve axons and other excitable membrane.

**Mechanism of action**

They act by **reversible blocking of the nerve conductance** which transmit feeling of pain from the locus to the brain. They **block sodium ion channels** and conduction of an action potential along the neuron would be prevented.

**Effect of PH**

Local anesthetics are weak bases and are usually formulated as the hydrochloride salt to render them water-soluble. At the chemical's pKa ionized and unionized forms of the molecule exist in an equilibrium but only the unionized molecule diffuses readily across cell membranes. Once inside the cell the local anesthetic will be in equilibrium, with the formation of the protonated (ionized form), which does not readily pass back out of the cell. This is referred to as "ion-trapping".

**Acidosis** such as caused by inflammation at a wound partly reduces the action of local anesthetics. This is partly because most of the anesthetic is ionized and therefore unable to cross the cell membrane to reach its cytoplasmic-facing site of action on the sodium channel.

**Methods of administration:**

- Surface topical
- Infiltration anaesthesia
- Intravenous regional anaesthesia
- Peripheral Nerve block
- Spinal anaesthesia
- Epidural anaesthesia

**Structure of Local anaesthetics**

1. **Lipophilic part**: (Carboyclic or heterocyclic ring) to pass through the non polar core of the cell membrane.

2. **Hydrophilic part**: To pass the inner polar face of the membrane of the cell which allow its solubility in extracellular and intracellular fluids.

3. **Ester or amide linker**: Both the ester and N-substituted amide functional groups are bioisosteres present in similar positions in the structures of local anesthetics.

4. **Intermediate chain**: (Short hydrocarbon chain). Ethylene is better than propylene which is more toxic, irritant and less active.

*They bind to their receptors by:*

1. Van der waal's forces (phenyl ring).
2. Hydrogen bond through the carbonyl group
3. Electrostatic or ionic bond with the onium ion of the tertiary alkylamino group.

**SAR**

1. **Lipophilic part**

   R= The electron donating group is essential for activity.
   Replacement with electron withdrawing groups (NO₂, CO, CN) will decrease the activity.
   - The electron donating group present in the ortho, para or both positions increases the activity and prolong the duration of action.
   - The O, O dimethyl (e.g. in Lidocaine) amide type protects it from hydrolysis and increases the duration of action.
   - The aromatic ring must be attached directly to carbonyl gp. If they are separated by –c (one carbon) or –c-c-(two carbons) results in inactive compound.

2. **Amide or ester link**

   The **amide resists the metabolic inactivation** more than ester which leads to longer duration of action.

3. **Bridge**

   Increasing the number of carbons decreases the potency.
4- Hydrophilic part

-Tertiary amine with a pKₐ between 7.5 and 9.0 \( \rightarrow \) At physiological pH, both the cationic and neutral form of the molecule exists

-The dialkyl gp attaching to nitrogen \((R_1,R_2)\) must be **identical**, they may be dimethyl (less active) or may be diethyl (active).

**Natural source:**
Coca leaves from which we extract the alkaloid cocaine which cause anesthesia to tongue. (chewing the leaves relieves pain).

**Classes of Local Anesthetics**

**I. The ester local anesthetic**
These include cocaine and benzoic acid esters.

   a. Cocaine:

   ![Cocaine structure](image)

   b. Esters of benzoic acid/Benzoyl esters

   1) Procaine: (prototype)
   N,N- Diethylaminoethyl ester of p-aminobenzoic acid.
   It is less potent with shorter duration of action than cocaine.
   Procaine lacks the local and systemic toxicities of cocaine.
   **Side effects:** Allergic reactions.
   Allergic reaction is seen with ester group due to hydrolysis into PABA (p-aminobenzoic acid) which leads to hypersensitivity reactions.

   2) Tetracaine:
   2-(Diethylamino)-ethyl-4-(butylamino)benzoate
   The most widely used ester type local anesthetic.
   It is more active (50 folds), longer duration than procaine.
   N- Alkylation increases the lipophilicity, increases electron donor strength.
2. Amide linkage

<table>
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<th>3) Bupivacaine</th>
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- Dimethyl protects the amide from hydrolysis so the duration of action increases since it decreases metabolism
- Longer duration and more rapid onset of action
  - Used for spinal anesthesia
- Longer duration and slow onset of action
  - Used for spinal anesthesia, epidural

**Synthesis of lidocaine**

\[
\text{CH}_3\text{C}_6\text{H}_4-\text{NH}_2 + \text{Cl-C-CH}_2-\text{Cl} \rightarrow \text{CH}_3\text{C}_6\text{H}_4-\text{NH-C-CH}_2-\text{Cl} \\
\text{HN(C}_2\text{H}_5)_2 \rightarrow \text{CH}_3\text{C}_6\text{H}_4-\text{NH-C-CH}_2-\text{N(C}_2\text{H}_5)_2
\]

- **4) Ropivacaine**
- **Advantage**
  1. Rapid/ faster onset,
  2. Long Duration of Action,
  3. Reversible & selective blockade of sensory nerves without motor blockade,
  4. Minimal local tissue irritation & no systemic toxicities (cardiac & CNS).