Intro to Neuromuscular blocking agents

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Quick Cholinergic review

• acetylcholine (ACH) is neurotransmitter of the parasympathetic nervous system.

• ACH is synthesized in the cholinergic neurons from choline and acetyl CoA then stored in synaptic vesicles then it will be release into synaptic gap to bind post synaptic receptors and lead to biological response
Figure 4.2
Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.
- 2 types of Cholinergic receptors:
  1) **Muscarinic** Receptor
  2) **Nicotinic** Receptor

Let’s talk shortly about each separately:

**Muscarinic Receptor**

- Muscarinic receptors action related to **postganglionic parasympathetic** (found on effector organ that innervated by parasympathetic).
- Muscarinic Receptor subdivided to:
  - **M\textsubscript{1}** receptor found in CNS & GI Glands (mainly there activation lead to ↑HCL in stomach).
  - **M\textsubscript{2}** receptor found in Heart.
  - **M\textsubscript{3}** receptor found in Smooth Muscle all over the body.
    ** all glands of the body are M\textsubscript{3} except GI gland M\textsubscript{1}
  - **M\textsubscript{4,5}** receptor found in CNS
In general stimulation of muscarinic receptors have 3 main effect:
1) Decrease Heart rate
2) Increase Secretion
3) Smooth muscle contraction

So far, it’s clear that when there is stimulation in
$M_1 \rightarrow$ Increase in HCL secretion.
$M_2 \rightarrow$ Decrease Heart rate
But when it comes to $M_3$ it have more than one effect since it’s located in SM all over the body.

** Muscarinic receptors agonist & antagonist are all **Non-selective** (so when we give agonist or antagonist we suspect effects in all the 3 types)

<table>
<thead>
<tr>
<th>Target</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye (sphincter)</td>
<td>Contraction $\rightarrow$ Miosis</td>
</tr>
<tr>
<td>Lungs (Bronchioles)</td>
<td>Contraction $\rightarrow$ bronchospasm</td>
</tr>
<tr>
<td>(Glands)</td>
<td>↑ Secretion</td>
</tr>
<tr>
<td>GIT (Stomach)</td>
<td>↑ Motility</td>
</tr>
<tr>
<td>(Intestine)</td>
<td>↑ contraction $\rightarrow$ Diarrhea</td>
</tr>
<tr>
<td>Bladder</td>
<td>1) contraction of bladder muscle</td>
</tr>
<tr>
<td></td>
<td>2) relaxation of the sphincter $\rightarrow$ urinary incontinence</td>
</tr>
<tr>
<td>Sphincters</td>
<td>Relaxation (except the lower esophageal sphincter $\rightarrow$ contraction)</td>
</tr>
<tr>
<td>Glands</td>
<td>↑ Secretion (↑ sweat, salivation, lacrimation)</td>
</tr>
<tr>
<td>Blood Vessels</td>
<td>Dilation $\rightarrow$ ↓BP</td>
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</tbody>
</table>
Nicotinic Receptor

• Nicotinic Receptor subdivided to 2 types:
  1) $N_N$ which found in $\rightarrow$ Adrenal gland & Autonomic Ganglia

  Note: we don’t want to mess with this type cuz it will lead to unspecific & undesirable effects.

  2) $N_M$ which found in $\rightarrow$ NMJ (neuromuscular junction)

  that mean it’s stimulation affect Skeletal Muscles.
Skeletal muscle relaxation can be produced by:

1. Deep inhalational anesthesia
2. Regional nerve block
3. Neuromuscular blocking agents a.k.a. (muscle relaxants)
Physiology of Neuromuscular Transmission

As a nerve’s action potential depolarizes its terminal → influx of calcium ions into the nerve cytoplasm → fuse of storage vesicles to terminal plasma membrane and release [ACh] → diffuse across the synaptic cleft to bind with nicotinic cholinergic receptors on a specialized portion of the muscle membrane, the motor end-plate.

Each neuromuscular junction contains approximately 5 million of these receptors, but activation of only about 500,000 receptors is required for normal muscle contraction.
Anticholinergic drugs
(Cholinergic blockers)

- anticholinergic drugs include:
  1. **Antimuscarinic agents** (atropine, ipratropium, scopolamine)
  2. Neuromuscular blockers (act on Nicotinic receptors in Somatic)
  3. Ganglionic blockers (act on Nicotinic receptor in ANS)
Antimuscarinic agents

• These agents
  1) **competitively** block muscarinic receptors.
  2) inhibit muscarinic functions.

• they are useful in different clinical situations, they have no actions on skeletal neuromuscular junctions or autonomic ganglia because they do not block nicotinic receptors.

• extent of Anticholinergic drugs effect depends on the degree of **baseline vagal tone**
Effect of antimuscarinic agents on the different organ systems:

• **Cardiovascular:**
  - Blockade of muscarinic receptors in the SA node produces **tachycardia**
  - **Transient slowing of heart rate** in response to smaller intravenous doses of atropine (<0.4 mg)
  - Large doses of anticholinergic agents can produce dilation of cutaneous blood vessels (**atropine flush**).

• **Respiratory:**
  - **inhibit respiratory tract secretions**, valuable property during airway endoscopic or surgical procedures.
  - **Relaxation of the bronchial smooth musculature** reduces airway resistance and increases anatomic dead space. (COPD & asthma)?
- CNS:
  - can cause a spectrum ranging from stimulation (excitation, restlessness, or Hallucinations) to depression (sedation and amnesia), depending on drug choice and dosage.
  - Cerebral depression, are prominent after scopolamine.
- GI:
  - ↓ Salivary secretions are. Gastric secretions are also decreased, but larger doses are necessary.
  - ↓ intestinal motility and peristalsis prolong gastric emptying time.
  - ↓ Lower esophageal sphincter pressure.

Overall, the anticholinergic drugs do not prevent aspiration pneumonia.
• Eye:
  - Topically → 1) Mydriasis  2) cycloplegia (an inability to accommodate to near vision)
  - Systemically → acute angle-closure glaucoma (rarely)

• Genitourinary:
  - urinary retention

• Thermoregulation:
Inhibition of sweat glands may lead to a rise in body temperature (atropine fever).
ATROPINE

• is a tertiary amine (can rapidly cross the BBB)
• **Dosage:**

atropine is administered IV or IM in a range of 0.01 to 0.02 mg/kg, up to the usual adult dose of 0.4 to 0.6 mg.

• **most efficacious** anticholinergic for treating bradyarrhythmias

• Patients with CAD may **not tolerate** the increased myocardial oxygen demand and decreased oxygen supply

• derivative of atropine, **ipratropium bromide**, is available in a metered-dose inhaler for the **treatment of bronchospasm** (limits systemic absorption)
• CNS effects of atropine are minimal after the usual doses.
• associated with mild postoperative memory deficits, and toxic doses are usually associated with excitatory reactions
• should be used cautiously in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder-neck obstruction
• IV atropine is used in the treatment of organophosphate pesticide & nerve gas poisoning
SCOPOLAMINE

• tertiary amine

• more potent antisialagogue (decrease production of saliva) than atropine and causes greater CNS effects

• Clinical dosages usually result in drowsiness & amnesia, although restlessness, dizziness, and delirium are possible.

• The lipid solubility allows transdermal absorption, and transdermal scopolamine (1 mg patch) has been used to prevent postoperative nausea and vomiting

• Because of its pronounced mydriatic effects, scopolamine is best avoided in patients with closed-angle glaucoma
GLYCOPHYRROLLATE

- **synthetic** product that differs from atropine in being a **quaternary amine**
- dose of glycopyrrolate is **one-half** that of atropine.
- Due quaternary structure, cannot cross the BBB and is almost **devoid** of CNS and ophthalmic activity.
- Potent **inhibition of salivary gland and respiratory tract secretions** is the primary rationale for using it.
- **Heart rate** usually **increases after IV**—but **not IM**.
- Glycopyrrolate has a **longer duration of action** than atropine (2–4 h versus 30 min after intravenous administration).
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<thead>
<tr>
<th></th>
<th>Atropine</th>
<th>Scopolamine</th>
<th>Glycopyrrolate</th>
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<tbody>
<tr>
<td>Tachycardia</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Bronchodilatation</td>
<td>++</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Sedation</td>
<td>+</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Antisialagogue effect</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

^0, no effect; +, minimal effect; ++, moderate effect; +++; marked effect.
• Any Questions so far?!