Neuromuscular blocking agents and Their antagonists

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Scope

- Clinical use
- Neuromuscular transmission
- Classification of neuromuscular blocking agents
  - Depolarizing drugs
  - Non-depolarizing drugs
- Factors affecting response to neuromuscular blockers
- Recovery from neuromuscular blockade
Clinical use

- NMBAs produce paralysis but does not ensure unconsciousness, amnesia and analgesia

- NMBAs are used to:
  - Improve condition to tracheal intubation.
  - Provide immobility during surgery.
  - Facilitate mechanical ventilation.
Neuromuscular transmission
Neuromuscular transmission
Classification of NMBAs

- NMBAs are divided into two classes:
  - Depolarizing NMBAs
  - Non-depolarizing NMBAs

- Distinctions between depo and non-depolarizing NMBAs:
  - Mechanism of action
  - Response to peripheral nerve stimulation
  - Reversal of block
## Classification of NMBAs

<table>
<thead>
<tr>
<th>Depolarizing drugs</th>
<th>Non-depolarizing drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of action</strong></td>
<td><strong>Chemical structure</strong></td>
</tr>
<tr>
<td>Short-acting</td>
<td>Aminosteroidal compound</td>
</tr>
<tr>
<td>- Succinylcholine</td>
<td>- Pancuronium</td>
</tr>
<tr>
<td>(Suxamethonium)</td>
<td>- Vecuronium</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>- Rocuronium</td>
</tr>
<tr>
<td>- Atracurium</td>
<td>- Pipercuronium</td>
</tr>
<tr>
<td>- Cisatracurium</td>
<td>Benzyllisoquinolinium</td>
</tr>
<tr>
<td>- Vecuronium</td>
<td>compound</td>
</tr>
<tr>
<td>- Rocuronium</td>
<td>- Atracurium</td>
</tr>
<tr>
<td>Long-acting</td>
<td>- Cisatracurium</td>
</tr>
<tr>
<td>- Doxacurium</td>
<td>- Pancuronium</td>
</tr>
<tr>
<td>- Pancuronium</td>
<td>- Pipercuronium</td>
</tr>
<tr>
<td>- Pipecuronium</td>
<td>- Mivacurium</td>
</tr>
</tbody>
</table>
**Mechanism of action**

- **Depolarizing drugs**
  - Act as ACh receptor agonists
  - Very closely resemble ACh, but are not metabolized by acetylcholinesterase
  - Bind to ACh receptors → generating prolonged depolarization of the muscle end-plate.
  - Continuous end-plate depolarization causes muscle relaxation
Mechanism of action

- Non-depolarizing drugs
  - Act as competitive antagonists to ACh receptors
  - Bind ACh receptors to prevent ACh from binding to its receptor and cannot induce end-plate depolarization
Reversal of neuromuscular blockade

- **Depolarizing drugs**
  - Not metabolized by acetylcholinesterase.
  - They diffuse away from the NMJ and are hydrolyzed in the plasma and liver by pseudocholinesterase.
  - This is a rapid process → short duration of action.
  - No specific agent to reverse a depolarizing blockade.
Reversal of neuromuscular blockade

- **Non-depolarizing drugs**
  - Not metabolized by either acetylcholinesterase or pseudocholinesterase, except mivacurium.
  - Reversal of their blockade depends on:
    - Redistribution
    - Gradual metabolism: Liver or chemical and enzymatic degradation.
    - Excretion of the relaxants by the body.
    - Administration of specific reversal agents
## Dosage guideline, Onset and Duration of action

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/kg)</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For intubation</td>
<td>For relaxation</td>
<td>Supplemental dose after intubation</td>
</tr>
<tr>
<td><strong>Depolarizing drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1.0 – 1.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Non-depolarizing drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.2 – 0.25</td>
<td>0.08 – 0.1</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.5 – 0.6</td>
<td>0.15 – 0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.15 – 0.2</td>
<td>0.04 – 0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1 – 0.2</td>
<td>0.03 – 0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6 – 1.0</td>
<td>0.15 – 0.3</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.08 – 0.12</td>
<td>0.03 – 0.05</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Depolarizing drug: Succinylcholine

- Succinylcholine is the only depolarizing NMBA in clinical use today.
- Physical structure:
  - Two joined ACh molecule.
  - Low lipid solubility

\[
\text{CH}_3\text{N}^+\text{CH}_2\text{CH}_2\text{O} - \text{C} - \text{C} - \text{CH}_2\text{CH}_2\text{O} - \text{C} - \text{O} - \text{CH}_2\text{CH}_2\text{N}^+\text{CH}_3 \quad [2 \text{Cl}^{-}]
\]
Depolarizing drug: Succinylcholine

- **Metabolism and Excretion**
  - Rapid metabolized by pseudocholinesterase → succinylmonocholine
  - As drug serum level fall → succinylcholine diffuse away from NMJ
  - Duration of action is prolonged by high dose or abnormal metabolism
Depolarizing drug: Succinylcholine

- Abnormal metabolism is due to:
  - Decrease rate of hydrolysis → hypothermia.
  - Low level or activity of acetylcholinesterase:
    - Pregnancy
    - Liver failure
    - Renal failure
    - Effect of some drugs: organophosphate, cholinesterase inhibitor
Depolarizing drug: succinylcholine

- Side effects and clinical consideration
  - Bradycardia
    - Stimulate nAChR in parasympathetic nervous system and mAChR in SA node
  - Fasciculation
  - Muscle pains
    - Postoperative myalgia
    - Most common in female and ambulatory anesthesia
    - May be due to unsynchronized contraction of muscle group
Depolarizing drug: succinylcholine

- Side effects and clinical consideration
  - Hyperkalemia
    - Normal muscle $\rightarrow$ succinylcholine induce increase serum $K^+$ $\sim$ 0.5 mEq/L
    - It can be life-threatening in patients with some conditions:
      - Preexisting hyperkalemia
      - Denervation injury
      - Prolong total body immobilization
      - Burn
      - Massive trauma
      - Severe abdominal infection
      - Myopathies
Depolarizing drug: succinylcholine

- Side effects and clinical consideration
  - Intragastric pressure elevation
    - Due to abdominal wall muscle contraction
    - Offset by an increase LES tone
  - Intraocular pressure elevation
  - Intracranial pressure elevation
    - Fasciculation stimulate muscle stretch receptor → increase cerebral activity → increase CBF and ICP
Depolarizing drug: succinylcholine

- Side effects and clinical consideration
  - Masseter muscle rigidity
    - Increase tone of masseter muscle → preventing laryngoscopy
    - MH??
  - Malignant hyperthermia (MH)
  - Histamine release
### Non-depolarizing drugs

#### Pharmacological characteristics

<table>
<thead>
<tr>
<th>Duration of action</th>
<th>Drugs</th>
<th>Renal excretion (%)</th>
<th>Biliary excretion (%)</th>
<th>Hepatic degradation (%)</th>
<th>Plasma hydrolysis</th>
<th>Hofmann elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Mivacurium</td>
<td>&lt; 10</td>
<td>NS</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>Atracurium</td>
<td>10</td>
<td>NS</td>
<td>0</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Cisatracurium</td>
<td>NS</td>
<td>NS</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Vecuronium</td>
<td>10-25</td>
<td>40-75</td>
<td>20-30</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Rocuronium</td>
<td>10-25</td>
<td>50-70</td>
<td>10-20</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Pancuronium</td>
<td>80</td>
<td>5-10</td>
<td>10</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Pipecuronium</td>
<td>70</td>
<td>20</td>
<td>10</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Doxacurium</td>
<td>70</td>
<td>30</td>
<td>?</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*NS = not significant*
Non-depolarizing drugs

Factors affect all non-depolarizing NMBAs:

- Temperature
  - Prolongs blockade by decreasing rate of hydrolysis and delaying excretion

- Acid-Base balance
  - Respiratory acidosis potentiates the blockade of most non-depolarizing relaxants
Non-depolarizing drugs

- Factors affect all non-depolarizing NMBAs:
  - Electrolyte abnormalities
    - Hypokalemia, hypocalcemia and hypermagnesemia potentiate non-depolarizing block
  - Age
    - Neonate increase sensitivity to non-depolarizing relaxants due to immature NMJ.
    - Neonates have greater extracellular volume than adult and elderly patients
Factors affect all non-depolarizing NMBAs:

- Drug interactions
  - Many drugs augment non-depolarizing relaxants
- Concurrent disease
  - Neurological or muscular disease can have profound effects on response to muscle relaxants
  - Diseases that alter metabolism and excretion of the drug may affect response to muscle relaxant.
## Non-depolarizing drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Depolarizing Blockade</th>
<th>Effect on Nondepolarizing Blockade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>+</td>
<td>+</td>
<td>Streptomycin, aminoglycosides, kanamycin, neomycin, colistin, polymyxin, tetracycline, lincomycin, clindamycin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>?</td>
<td>-</td>
<td>Phenytoin, carbamazepine, primidone, sodium valproate</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>+</td>
<td>+</td>
<td>Quinidine, calcium channel blockers</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>+</td>
<td>-</td>
<td>Neostigmine, pyridostigmine</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>?</td>
<td>+</td>
<td>Used in treatment of malignant hyperthermia (has quaternary ammonium group)</td>
</tr>
<tr>
<td>Inhalational anesthetics</td>
<td>+</td>
<td>+</td>
<td>Volatile anesthetics</td>
</tr>
<tr>
<td>Ketamine</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>+</td>
<td>+</td>
<td>High doses only</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>+</td>
<td>?</td>
<td>Prolongs onset and duration of succinylcholine</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>+</td>
<td>+</td>
<td>Doses used to treat preeclampsia and eclampsia of pregnancy</td>
</tr>
</tbody>
</table>
## Non-depolarizing drugs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Response to Depolarizers</th>
<th>Response to Nondepolarizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Contracture</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Autoimmune disorders (systemic lupus erythematosus, polymyositis, dermatomyositis)</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Burn injury</td>
<td>Hyperkalemia</td>
<td>Resistance</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Slight hypersensitivity</td>
<td>Resistance</td>
</tr>
<tr>
<td>Familial periodic paralysis (hyperkalemic)</td>
<td>Myotonia and hyperkalemia</td>
<td>Hypersensitivity?</td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
<td>Hyperkalemia</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>Hyperkalemia</td>
<td>Resistance on affected side</td>
</tr>
<tr>
<td>Muscular denervation (peripheral nerve injury)</td>
<td>Hyperkalemia and contracture</td>
<td>Normal response or resistance</td>
</tr>
<tr>
<td>Muscular dystrophy (Duchenne type)</td>
<td>Hyperkalemia and malignant hyperthermia</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Resistance and proneness to phase II block</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Myasthenic syndrome</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Myotonia (dystrophica, congenita, paramyotonia)</td>
<td>Generalized muscular contractions</td>
<td>Normal or hypersensitivity</td>
</tr>
<tr>
<td>Severe chronic infection (tetanus, botulism)</td>
<td>Hyperkalemia</td>
<td>Resistance</td>
</tr>
</tbody>
</table>
Non-depolarizing drugs: Benzylisoquinolinium compound

- Atracurium

- **Metabolism and excretion**
  - Independent of renal and hepatic function
  - < 10% is excreted unchanged by renal and biliary routes

- Ester hydrolysis
  - Catalyzed by nonspecific esterases
Non-depolarizing drugs: Benzylisoquinolinium compound

- **Atracurium**
  - **Metabolism and excretion**
    - Hofmann elimination
      - A spontaneous nonenzymatic chemical breakdown.
      - Depend on physiological pH and temperature.
      - The metabolites are Laudanosine (CNS excitation) and monoquaternary acrylate.
    - The metabolites have no neuromuscular blocking activity.
Non-depolarizing drugs: Benzylisoquinolinium compound

- Atracurium
  - Side effects and clinical consideration
    - Hypotension and tachycardia
      - Histamine release
      - Rapid injection of large dose
      - Slow rate of injection minimizes these effects
    - Bronchospasm
      - Histamine release
      - Severe bronchospasm is possible even in patients without a history of asthma
Non-depolarizing drugs: Benzylisoquinolinium compound

- Atracurium
  - Side effects and clinical consideration
    - Laudanosine toxicity
      - CNS excitation and precipitate seizures
      - Metabolized by liver and excreted in urine and bile
      - Consider in patient who receive extremely high total dose (prolong infusion) or has hepatic failure
    - Temperature and pH sensitivity
      - Hypothermia → decrease rate of hydrolysis → prolong duration
      - Acidosis → prolong duration
Non-depolarizing drugs: Benzylisoquinolinium compound

- Atracurium
  - Side effects and clinical consideration
    - Chemical incompatibility
      - Precipitate in alkaline solution such as thiopental
    - Allergic reactions
Non-depolarizing drugs: Benzylisoquinolinium compound

- Cisatracurium
  - Metabolism and excretion
    - Hofmann elimination
    - Nonspecific esterases do not appear to be involved in the metabolism of cisatracurium
  - Side effects and clinical consideration
    - Does not produce histamine release
    - Does not effect HR and blood pressure
    - Laudanosine toxicity
    - pH and temperature sensitivity
    - Chemical incompatibility
Non-depolarizing drugs: Aminosteroid compound

- **Pancuronium**
  - **Metabolism and excretion**
    - Renal excretion ~ 80% (unchange form)
    - Biliary excretion ~ 10%
    - Deacetylated by the liver ~ 10% → metabolic products have some neuromuscular blocking activity
    - Carefully use in renal failure patients → prolong duration
    - Patients with cirrhosis → require higher initial dose due to increase Vd but have lower maintenance dose due to decrease plasma clearance
Non-depolarizing drugs: Aminosteroid compound

- Pancuronium
  - Side effects and clinical consideration
    - Hypertension and tachycardia
      - Vagal blockade (Vagolytic effect)
      - Sympathetic stimulation
        - Ganglionic stimulation
        - Increase catecholamine release from adrenergic nerve ending
        - Decrease catecholamine reuptake
    - Use with caution or avoid in patient whom an increase HR would be particularly detrimental
Non-depolarizing drugs: Aminosteroid compound

- Pancuronium
  - Side effects and clinical consideration
    - Arrhythmias
      - Increase AV conduction and increase catecholamines release → ventricular arrhythmias in some patients
    - Allergic reactions
      - Hypersensitivity to bromide
    - Chemical incompatibility
Non-depolarizing drugs: Aminosteroid compound

- Vecuronium
  - Metabolism and excretion
    - Biliary excretion ~ 40-75%
    - Renal excretion ~ 15-25%
    - Metabolized by the liver ~ 20-30% → active metabolites
    - Long-term use result in prolong duration
Non-depolarizing drugs: Aminosteroid compound

- Vecuronium

  - Side effects and clinical consideration
    - Cardiovascular
      - Good CVS stability
      - But bradycardia may be observed in combination with opioid
    - Liver failure
      - Vecuronium is not significantly prolonged in cirrhosis unless dose greater than 0.15 mg/kg are given
Non-depolarizing drugs: Aminosteroid compound

- Rocuronium
  - Metabolism and excretion
    - Excrete primarily by liver and slightly by kidneys (60 and 20%)
    - Slightly metabolized by liver ~ 10-20%
    - Duration of action is moderately prolonged by severe hepatic failure, but not significantly affected by renal failure
Non-depolarizing drugs: Aminosteroid compound

- Rocuronium
  - Side effects and clinical consideration
    - At dose 0.9-1.2 mg/kg → rapid onset → alternative for rapid-sequence induction
    - Has slight vagolytic effect
    - Chemical incompatibility
Recovery from neuromuscular blockade

- Assessment of neuromuscular blockade
  - Clinical evaluation
  - Evoked responses to peripheral nerve stimulation
## Recovery from neuromuscular blockade

<table>
<thead>
<tr>
<th>Clinical test</th>
<th>Acceptable clinical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained bite (Corresponds to TOF ratio of 0.85)</td>
<td>Sustained jaw clench on tongue blade (Very reliable with patient cooperation)</td>
</tr>
<tr>
<td>Hand grip</td>
<td>Sustained at a level qualitatively similar to preinduction baseline</td>
</tr>
<tr>
<td>Head lift</td>
<td>Perform unaided with patient supine for 5s</td>
</tr>
<tr>
<td>Inspiratory force</td>
<td>At least -40 cmH$_2$O</td>
</tr>
<tr>
<td>VC</td>
<td>At least 20 ml/ kg</td>
</tr>
<tr>
<td>$V_T$</td>
<td>At least 5 ml/ kg</td>
</tr>
<tr>
<td>TOF</td>
<td>No palpable fade or TOF ratio &gt; 0.9 is accepted for extubation</td>
</tr>
<tr>
<td>DBS</td>
<td>No palpable fade</td>
</tr>
</tbody>
</table>
Recovery from neuromuscular blockade

- Major determinants of speed and adequacy of reversal
  - Depth of block at the time of antagonist administration
  - The antagonist administered
  - Dose of antagonist
  - Rate of spontaneous recovery from the NMBAs
  - Concentration of inhaled anesthetic present during reversal
Recovery from neuromuscular blockade

- Other factors that may interfere with antagonism
  - Acid-Base status
  - Electrolyte imbalance
  - Hypothermia
  - Drug interaction
Recovery from neuromuscular blockade

- Antagonism of residual neuromuscular blockade
  - Anticholinesterase
    - Neostigmine
    - Edrophonium
    - Pyridostigmine
Recovery from neuromuscular blockade

- **Antagonism of neuromuscular blockade**
  - **Mechanism of antagonism**
    - Increase the concentration of ACh at the motor end-plate by:
      - Inhibiting acetylcholinesterase
      - Increase ACh release from presynaptic nerve terminal
    - The increase amount of ACh compete with the non-depolarizing agent → reestablishing normal neuromuscular transmission
Recovery from neuromuscular blockade

- Side effects of anticholinesterase
- Effects of anticholinesterase on mAChR

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Muscarinic side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Decrease HR, Bradyarrhythmias</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Bronchospasm, bronchial secretion</td>
</tr>
<tr>
<td>GI</td>
<td>Intestinal spasm, increase salivation</td>
</tr>
<tr>
<td>GU</td>
<td>Increase bladder tone</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Pupillary constriction</td>
</tr>
</tbody>
</table>
Recovery from neuromuscular blockage

- Side effects of anticholinesterase
  - The muscarinic side effects must be blocked with anticholinergic drugs (Atropine or Glycopyrrolate)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/ kg)</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Recommended anticholinergic</th>
<th>Dose of anticholinergic (mg/ kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium</td>
<td>0.5-1.0</td>
<td>2</td>
<td>45-60</td>
<td>Atropine</td>
<td>0.02</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>0.04-0.07</td>
<td>7</td>
<td>60-90</td>
<td>Glycopyrrolate</td>
<td>0.007-0.015</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>0.15-0.25</td>
<td>11</td>
<td>60-120</td>
<td>Glycopyrrolate</td>
<td>0.007-0.015</td>
</tr>
</tbody>
</table>
Recovery from neuromuscular blockade

- Other limitations of anticholinesterase:
  - Reversal may not be completely achieved.
  - Only effective if given when partial spontaneous recovery has already occurred.
  - No reliable method of reversing profound neuromuscular blockade.
THANK YOU FOR YOUR ATTENTION