Pharmacology of Local Anesthetics

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Local Anesthetics (LAs)

• Definition: drugs that cause loss of sensation without loss of consciousness
• Reversibly block nerve conduction
• Act on every type of nerve fiber
• Also act on cardiac muscle, skeletal muscle and the brain
• No structural damage to the nerve cell
Peripheral Nerve Fibers

- **A_\alpha** and **A_\beta**:  
  - Large diameter, myelinated  
  - Motor and proprioception
- **A_\gamma**: Smaller diameter, myelinated  
  - Muscle tone
- **A_\delta**: Smallest myelinated  
  - Pain, temperature, touch
- **B**: Preganglionic sympathetic
- **C**: Unmyelinated: Sensory: Pain, temperature, touch

*Electron micrograph of peripheral nerve*
Relative Size and Susceptibility of Different Types of Nerve Fibers to Local Anesthetics.

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Function</th>
<th>Diameter (μm)</th>
<th>Myelination</th>
<th>Conduction Velocity (m/s)</th>
<th>Sensitivity to Block</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>Proprioception, motor</td>
<td>12–20</td>
<td>Heavy</td>
<td>70–120</td>
<td>+</td>
</tr>
<tr>
<td>Beta</td>
<td>Touch, pressure</td>
<td>5–12</td>
<td>Heavy</td>
<td>30–70</td>
<td>++</td>
</tr>
<tr>
<td>Gamma</td>
<td>Muscle spindles</td>
<td>3–6</td>
<td>Heavy</td>
<td>15–30</td>
<td>++</td>
</tr>
<tr>
<td>Delta</td>
<td>Pain, temperature</td>
<td>2–5</td>
<td>Heavy</td>
<td>5–25</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Type B</strong></td>
<td></td>
<td>&lt; 3</td>
<td>Light</td>
<td>3–15</td>
<td>++++++</td>
</tr>
<tr>
<td><strong>Type C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal root</td>
<td>Pain</td>
<td>0.4–1.2</td>
<td>None</td>
<td>0.5–2.3</td>
<td>++++</td>
</tr>
<tr>
<td>Sympathetic</td>
<td>Postganglionic</td>
<td>0.3–1.3</td>
<td>None</td>
<td>0.7–2.3</td>
<td>++++</td>
</tr>
</tbody>
</table>
Action site: voltage-gated Na⁺ channels
Use-dependent Blockade
Actions of LAs

- Ionic gradient and resting membrane potential are unchanged
- Decrease the amplitude of the action potential
- Slow the rate of depolarization
- Increase the firing threshold
- Slow impulse conduction
- Prolong the refractory period
CNS Toxicity

- Correlation between potency and seizure threshold
  - Bupivacaine
    - 2 μg/ml
  - Lidocaine
    - 10 μg/ml

TOXIC EFFECTS

- CVS depression
- Respiratory arrest
- Coma
- Convulsions
- Unconsciousness
- Muscular twitching
- Visual disturbance
- Lightheadedness
- Numbness of tongue
Cardiovascular Toxicity

- Attributable to their direct effect on cardiac muscle

- Contractility
  - Negative inotropic effect that is dose-related and correlates with potency
  - Interference with calcium signaling mechanisms

- Automaticity
  - Negative chronotropic effect

- Rhythmicity and Conductivity
  - Ventricular arrhythmias
### Structural Classes: Esters and Amides

<table>
<thead>
<tr>
<th>Esters</th>
<th>Lipophilic Group</th>
<th>Intermediate Chain</th>
<th>Amine Substituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine (Novocain)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracaine (Pontocaine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzocaine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All are weak bases:

\[ BH^+ \rightleftharpoons B + H^+ \]
Amides

Lidocaine (Xylocaine)
利多卡因

Mepivacaine (Carbocaine, Isocaine)
甲哌卡因

Bupivacaine (Marcaine),
levobupivacaine (Chirocaine)
布比卡因

Etidocaine (Duranest)
布比卡因

Prilocaine (Citanest)
丙胺卡因
Pharmacokinetics

Absorption (injected or topical)
- affected by vascularity
- presence of additional vasoconstrictor
- Duration prolonged by vasoconstrictor (epinephrine)
  - localizes agent to site of action
  - contraindicated in extremities
- Systemic Toxic Effects: CNS, cardiovascular
Pharmacokinetics

Distribution
- LAs bind in the blood to a1-glycoprotein and albumin

• Alpha phase (快速吸收相) – rapidly redistributed to well-perfused tissues

• Beta phase (再分布相) – distribution to less perfused or slowly equilibrating tissues

• Gamma phase (消除相) – clearance representing metabolism and excretion
Pharmacokinetics

Metabolism

• Esters (rapid)
  – Metabolized by plasma cholinesterases
  – Rapid plasma degradation
  – Produce PABA (para-aminobenzoic acid), important in allergy

• Amides (slower)
  – Hepatic metabolism
  – Allergy very rare
  – Longer plasma half-life

\[ \text{Esters} \downarrow \quad \text{Amides} \downarrow \]
\[ \text{plasma cholinesterases (shorter } t_{1/2} \text{)} \quad \text{liver (longer } t_{1/2} \text{)} \]
Modes of Administration

- topical
- local infiltration (intradermal)
- peripheral/specific nerve or field block
- epidural anesthesia
- spinal anesthesia (subarachnoid space)
Uses of local anesthesia

Topical local (surface) anesthesia: for eye, ear, nose, and throat procedures and for cosmetic surgery

Infiltration anesthesia: local injection around the region to be operated.

Conduction anesthesia: local injection around the peripheral nerve trunk

Epidural anesthesia: local injection into the epidural space

Subarachnoid anesthesia or Spinal anesthesia: local injection into the cerebrospinal fluid in subarachnoid cavity
Adverse reactions

• Toxicity: CNS, CVS

• Allergic Reactions
   Metabolite of “ester” LAs
    – Para-aminobenzoic acid
    – Allergen
   Allergy to “amide” LAs is extremely rare
Lidocaine

- One of the most widely used local anesthetics
- Rapid onset, medium duration
- Also available in ointment (软膏), jelly (凝胶), and aerosol (喷雾剂)
- Other uses: anti-arrhythmic
Eutectic Mixture of Local Anesthetic (EMLA)

- Contains lidocaine (2.5%), prilocaine (2.5%), emulsifier, thickener, distilled water

(a eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals)

- Must be applied one hour prior to procedure
Pharmacology of General Anesthetics
WHAT IS ANESTHESIA?

• Anesthesia is necessary for some diagnostic, therapeutic, and surgical intervention.

• The physiologic state induced by general anesthetics typically includes analgesia, amnesia, loss of consciousness, inhibition of sensory and autonomic reflexes, and skeletal muscle relaxation.

• Types of General Anesthesia: Inhaled Anesthetics (gases or “vapors”), Intravenous Anesthetics (be given intravenously).
Site of action

• Probably on synaptic transmission
• Do they act at one site (*unitary hypothesis*) or at multiple sites?
• Do they act via the biochemical milieu or, like many other drugs, at protein receptors?
Inhaled anesthetics

• Many different, apparently unrelated molecules produce general anesthesia – inert gases, simple inorganic & organic compounds, more complex organic compounds

• Characteristics – rapid onset, rapid reversibility, relationship between lipid solubility & potency
Stages of anesthesia (ether)

• Stage I: analgesia – sensory block in spinal cord
• Stage II: paradoxical excitation due to loss of some inhibitory tone and direct stimulation of excitatory transmission
• Stage III: surgical anesthesia – block of the ascending reticular activating system
• Stage IV: failure – cardiovascular and respiratory collapse due to inhibition
Signs for anesthetic depth

**TOO LIGHT**
- Tachycardia
- Hypertension
- Eyelid reflex
- Lacrimation
- Swallowing
- Laryngospasm
- Movement

**TOO DEEP**
- Hypotension
- Organ failure
Nitrous Oxide

Gas at room temperature
Volatile liquids at room temperature

Diethyl Ether
(乙醚)

Halothane
(氟烷)

Isoflurane
(异氟醚)

Desflurane
(地氟醚)
Inhaled anesthetic delivery system
Vaporizing the anesthetic liquid
Gas flowmeters
Mask
• Higher blood solubility is shown as a larger blood box
• Higher solubility means gas rapidly moves into blood, but concentration that reaches brain increases more slowly
MAC – minimum alveolar anesthetic concentration

MAC is the anesthetic concentration that produces immobility in 50% of patients exposed to a noxious stimulus.

Addition of MAC
Factors that alter MAC

• **Increase MAC** – Being young, hyperthermia, chronic ETOH, CNS stimulants, hyperthyroidism

• **Decrease MAC** – Old age, hypothermia, acute ETOH, CNS depressant drugs including narcotics & benzodiazepines
<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Blood:Gas Partition Coefficient</th>
<th>Brain:Blood Partition Coefficient</th>
<th>Minimal Alveolar Concentration (MAC) (%)</th>
<th>Metabolism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>0.47</td>
<td>1.1</td>
<td>&gt; 100</td>
<td>None</td>
<td>Incomplete anesthetic; rapid onset and recovery</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>1.3</td>
<td>6–7</td>
<td>&lt; 0.05%</td>
<td>Low volatility; poor induction agent (pungent); rapid recovery</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.69</td>
<td>1.7</td>
<td>2.0</td>
<td>2–5% (fluoride)</td>
<td>Rapid onset and recovery; unstable in soda-lime</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.40</td>
<td>2.6</td>
<td>1.40</td>
<td>&lt; 2%</td>
<td>Medium rate of onset and recovery</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.80</td>
<td>1.4</td>
<td>1.7</td>
<td>8%</td>
<td>Medium rate of onset and recovery</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.30</td>
<td>2.9</td>
<td>0.75</td>
<td>&gt; 40%</td>
<td>Medium rate of onset and recovery</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>12</td>
<td>2.0</td>
<td>0.16</td>
<td>&gt; 70% (fluoride)</td>
<td>Very slow onset and recovery</td>
</tr>
</tbody>
</table>
General characteristics

• Analgesia – weak except for nitrous oxide
• Potency – high, except for nitrous oxide
• Muscle Relaxation – some, but weak
• Airway irritation – desflurane (地氟醚) worst, sevoflurane (七氟烷) best tolerated
• Primary effect on conductive tissue – inhibitory
• Primary effect on smooth muscle – relaxation
Effects on brain

- Transition to unconsciousness \( \equiv 0.4 \text{ MAC} \)
- \( \downarrow \text{O}_2 \) consumption but \( \uparrow \text{Cerebral Blood Flow} \) means potential injury with brain tumors/head injury (\( \uparrow \text{pressure} \))
Effects on ventilation

- **Respiratory Rate**: ↑
- **Tidal Volume**: ↓
- **Ventilation**: ↓
- **PaCO₂**: ↑
- **Hypoxia Risk**: ↑

*Data are mean ± SE*
Liver toxicity

• “Halothane Hepatitis”
• Incidence post Halothane – 0.003%
• Symptoms – fever, anorexia (胃口不好), nausea & vomiting that occur 2 - 5 days post-op
• Blood – eosinophilia; altered liver function
• Rare – liver failure & death
Malignant hyperthermia

- Hypermetabolic syndrome – hyperthermia, $\uparrow \text{CO}_2$, tachycardia, cyanosis, muscle rigidity
- Triggered by halogenated anesthetics & depolarizing muscle relaxants
- Familial relationship, i.e. genetic heterogeneity
  - mutation in Ca$^{2+}$ reuptake
- Incidence, $\sim 1/14,000$ anesthesia (0.01%)
- Specific Treatment – Dantrolene (inhibit Ca$^{2+}$ release from the sarcoplasmic reticulum)
Nitrous oxide toxicity

- Bone Marrow Depression – megaloblastic, inhibition of $B_{12}$ dependant enzymes
- Peripheral neuropathy
- Expansion of closed air spaces – bowel obstruction, pneumothorax, bullous emphysema, middle ear obstruction, pneumocephalus
- CNS injury – adults & neonates
NITROUS OXIDE KILLS NEURONS IN THE YOUNG AND THE OLD

- Developing rat brain
- Exposure to a combination including nitrous, isoflurane & midazolam
- Persistent learning deficits
Intravenous Anesthetics
Usually activate GABA_A receptors

- Thiopental (硫喷妥)
- Propofol (异丙酚)
- Etomidate (依托咪酯)
- Midazolam (咪达唑仑)
- Ketamine (氯胺酮)
Redistribution of thiopental after an intravenous bolus administration
Combination of Anesthetics

• Premedication
• Basal anesthesia
• Induction of anesthesia
• skeletal muscle relaxants
• neuroleptanesthesia