Anesthetics

Locals and Generals

http://wings.buffalo.edu/aru/preprohibition.htm
Overview

- **Local anesthetics**
  - Esters
  - Amides

- **General anesthetics**
  - Parenteral
    - Barbiturates
    - Non-barbiturates
  - Inhalation
    - Volatile liquids
    - Gases

- **Analgesia**
  - Selective pain loss or prevention

- **Anesthesia**
  - Goal = loss of all sensation
  - Locals - block PNS (but can affect ANY neuron, anywhere - $\otimes Na^+$ channel)
  - Generals - block CNS (by various & ill-defined mechanisms)
Local Anesthesia Overview

• Progression of anesthesia related to:
  – Diameter, myelination & conduction velocity of neurons.

• Sensation lost in this order:
  • Pain
  • Temperature
  • Touch
  • Proprioception
  • Skeletal muscle tone

• Ester-types (e.g., benzocaine)
  – Esterase metabolism to PABA (para-aminobenzoic acid) derivatives (allergens!)

• Amide-types (e.g., lidocaine)
  – P450 & Phase II metabolism to polar molecules

• Mechanism
  – Reversible ⊗ of AP conduction by binding to voltage gated Na+ channel (usually)

• Weak bases (HCl-salts)
Locals:  *Adverse effects*

- **CNS**
  - Depression, nausea, headache, seizures, coma
  - *Post dural puncture headache occurs in 10-40% of lumbar puncture patients because of CSF leaking from a hole in the dura into the epidural space.*
- **CV**
  - Hypotension, cardiac depression
- **PNS**
  - Autonomic ganglia blockage can cause smooth and skeletal muscle relaxation (flaccid paralysis)
- **Allergic reactions**
  - Ester-types metabolized to PABA

- Systemically absorbed locals can cause fatal CNS effects
- When injected SC
  - EPI added to cause vasoconstriction

On 16 Jan 2009, FDA issued a warning regarding the use of *topical anesthetics on large skin areas* & the potential to cause arrhythmias, seizures, breathing difficulties, coma or death

*Saran-type wraps, or hydrocolloids (e.g., DuoDerm, TegaDerm) are commonly applied over topicals to ↑ absorption*
Locals - Ester-type Drugs

Generic name contains one “i”

• Cocaine
  – Plant alkaloid, both local anesthetic and CNS stimulant
  – Only local to cause vasoconstriction

• Procaine
  – 1st local created after cocaine discovered
  – Metabolized to PABA
  – Low potency, short duration, no topicals

• Benzocaine (Anbesol)
  – Common OTC topical cream, lozenge, drops & spray
  – Indicated for temporary relief of minor pain & itch. Anti irritant for gums, throat, skin and ears.
  – Don’t use if patient has methemoglobinemia

Miscellaneous locals: dyclonine (Cepacol, Sucrets) & pramoxine (Caladryl)
Coca-Cola stopped adding cocaine by 1929, around the same time 7-UP removed lithium...but there never was much anyway.

Note the use as an antiemetic! Dr Pepper and 7-UP also started as patent-medicines. Coke works best as an antiemetic if de-gassed & at room temperature. Must be the “Classic” formula of Coca-Cola.
Locals - Amide-type Drugs

- **Lidocaine (Xylocaine) & Etidocaine**
  - Widely used topical, infiltrate, nerve block, epidural and spinal anesthetic

- **Bupivacaine, mepivacaine, ropivacaine…**
  - Similar, various durations. The levo- isomer of bupivacaine used in labor and delivery

- **Prilocaine**
  - Congener of lidocaine
  - Toxic metabolite limits use to topicals and infiltrates

**Lidocaine indications and uses:**
Ventricular arrhythmias, itching, burning and pain from skin inflammation; dental & minor surgery anesthetic; tinnitus; to numb the skin and reduce nematocyst firing from jellyfish stings

Generic name contains two “i’s”
Local Anesthetics

~20% of nerve blocks → nerve damage
– Neurotoxicity due to allergy (esters)
– XS fluid pressure
– Severing of nerve with needle
– Hematoma pressure
– Infection leading to inflammation

EMLA cream
– Eutectic mixture of 2.5% lidocaine and 2.5% prilocaine
– EMLA
  • Eutectic Mixture of Local Anesthetics
– Eutectic
  • A combination of chemicals that exists as a solid at a lower temperature than any other combination of those chemicals
General Anesthesia

• Goals
  – Loss of the ability to
    • Move *(Immobilization)*
    • Feel pain *(Analgesia)*
    • Remember the event *(Amnesia)*
Balanced Anesthesia: Stages

• Effects
  – Stage I
    • ⊗ spinal cord neurons, analgesia & sedation occurs
    • Induction usually accomplished with parenteral (propofol)
  – Stage II
    • ⊗ of inhibitory (GABA) neurons may cause paradoxical excitation
  – Stage III
    • Reticular-activating system ⊗, consciousness lost and spinal reflexes ⊗ - “Surgical anesthesia” (*RAS – covers midbrain, thalamus & hypothalamus*)
    • Maintenance often accomplished with inhaled anesthetics
    • Recovery: between the end of anesthesia & the development of consciousness with the ability to move & communicate.
  – Stage IV
    • CNS depression, CV depression - patient over anesthetized
The Anesthetic State: a collection of changes

- Amnesia
- Immobility to noxious stimuli
- Attenuation of autonomic responses to noxious stimuli
- Analgesia
- Unconsciousness

Anesthesia is almost always accomplished using a “cocktail” of drugs, each of which provides an element of the anesthetic state: e.g., midazolam provides amnesia and sedation; the NMJ blockers immobilize the patient.... Ketamine is one of the few agents that may be used solo.
Balanced (General) Anesthesia

- **Pre-op medications**
  - Anticholinergic antispasmodics reduce secretions & GI mobility
    - Hyoscyamine, dicyclomine, glycopyrrolate, propantheline, scopolamine, atropine
  - NMJB prevent unwanted movement, allow intubation
    - Pancuronium, succinylcholine
- **Sedative hypnotics**
  - BZD also ensure amnesia
- **Antiemetics**
  - Ondansetron, dexamethasone, metoclopramid, droperidol
- **Antihistamines**
  - Besides drying secretions, sedation and anxiolysis may be enhanced
    - Hydroxyzine, diphenhydramine
- **Narcotics**
  - Analgesia & sedation, but also apnea, movement & rigidity
    - Fentanyl, meperidine, sufentanil (labor & delivery), alfentanil, remifentanil
- **General Anesthetics**
  - Most are NOT analgesic
  - All are parenteral, some injections, some inhalation
Contraindications to General Anesthesia

- Impaired liver or kidney function
- Status asthmaticus *(Except Halothane!)*
- Myasthenia gravis
- Malignant hyperthermia (MH) history (family or patient)
- CV or lung disease (other than, or in addition to, asthma)
- Lack of adequate vein access for IV
- Hypotension or shock

General anesthesia associated with SIADH and MH*

* SIADH = syndrome of inappropriate ADH secretion
MH = malignant hyperthermia
Focus on: Malignant Hyperthermia

- Autosomal dominant gene
- Triggered by anesthetics
  - All halogenated volatile anesthetics
  - Most gas anesthetics
  - Succinylcholine
- Prevent/Treat with dantrolene (Dantrium)
- Uncontrolled skeletal muscle oxidative metabolism
  - Muscle rigidity, tachycardia, hyperthermia

Dantrolene Sodium

Indicated for chronic spasticity (spinal injury, cerebral palsy, MS) & malignant hyperthermia

- Hepatotoxic
- Watch for signs of hepatitis
- Estrogen ↑ risk of liver damage
- Hepatitis, diarrhea, drowsiness, fatigue, constipation, insomnia, sweating, arrhythmias, depression, excessive secretions, abnormal hair growth, blurry vision, seizures, urinary retention, sexual dysfunction
- COPD, CHD, liver disease

PO, IV

A Beale

PHRM 203 - Anesthetics
## Parenteral General Anesthetics: Barbiturates

*Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karch. Lippincott, Williams & Wilkins. 2008*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methohexital (Brevital)</td>
<td>Rapid</td>
<td>Ultra, ultrashort</td>
</tr>
<tr>
<td>Thiopental (Pentothal)</td>
<td>Rapid</td>
<td>Ultrashort</td>
</tr>
</tbody>
</table>

**NOTE:** Sodium thiopental was one of several medications used in States with the death penalty (death by lethal injection). That fact led the only FDA-approved manufacturer, Hospira, an Italian company, to [*cease production* of injectable thiopental for use in the United States in 2011. Abbott, an FDA-approved manufacturer of a thiopental suspension for rectal administration, has also discontinued production. Baxter, a distributor for Hospira, no longer lists thiopental in their product list. (7/2014)]

According to the American Society of Anesthesiologists, sodium thiopental is a 1st line anesthetic agent, especially for geriatric neurologic, cardiovascular and obese patients.

---

A Beale

PHRM 203 - Anesthetics

15
Parenteral General Anesthetics: *Non-Barbiturates*

Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karch. Lippincott, Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate (Amidate)</td>
<td>1 min</td>
<td>3-5 minutes</td>
</tr>
<tr>
<td>Ketamine (Ketaset, Ketalar) C-III</td>
<td>Rapid</td>
<td>45 minutes</td>
</tr>
<tr>
<td>Propofol (Diprivan)</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
</tbody>
</table>

**Etomidate (Amidate)**

Hypnotic without analgesia but lots of transient muscle movement!

Indicated for induction of general anesthesia

*IV hypnosis within 1 minute*

- Transient venous pain at IV site & myoclonus; Hyper- or hypoventilation, short duration apnea, laryngospasm, hiccups, BP lability, arrhythmias, nausea & vomiting
- Rapid injection causes severe hypotension
Ketamine (Ketalar, Ketaset) C-III

- Rapid-acting dissociative anesthetic
  - Induction within 30 seconds
  - Profound analgesia
  - Normal pharyngeal-laryngeal reflexes
    - Laryngospasm possible
    - Control with midazolam or diazepam
  - Normal to slightly increased skeletal muscle tone
  - Increased blood pressure and respiration rate
  - Very wide safety margin
    - 10X dose with full recovery

- **Indications**
  - **Sole anesthetic**
  - **Adjuvant (to nitrous oxide)**
  - **Induction**

Ketamine = anesthetic of choice for asthmatics – It relaxes bronchial smooth muscle

Off label uses:
  - Chronic pain
  - Neuropathic pain
**Ketamine (Ketalar, Ketaset) C-III**

- **Emergence reaction in adults!**
  - 12% of patients
  - Age-related, very young and old least affected

- **Adverse reactions:**
  - ~50% of adults have CNS effects - delirium, hallucinations, irrational thoughts & behavior, including violent reactions to sounds in the surgery!
  - ↑ BP & HR (sympathomimetic).
  - May cause seizures.

- **Post-op confusion**
  - No driving for 24 hours

- **Enhances CNS depression of other CNS agents**
Fentanyl (Sublimaze, Duragesic)

• Potent opioid agonist C-II (addictive)
  – See Pain Lecture for more information
• Boxed warnings
  1. Not for the opioid naïve
  2. May cause fatal respiratory depression
  3. May be fatal to kids
  4. Not for post op headaches
  5. Not to be used on broken skin (TD)
  6. Contains a C-II drug
• Analgesia, sedation, induction, and anesthesia for minor procedures. No amnesia or unconsciousness
  – IV or epidural administration

PO (tablet, lozenge, buccal, soluble film), TD, IV, IM, etc.

May cause chest wall rigidity and (a lot of) skeletal muscle movement; large doses cause apnea which persists long after analgesia ends
• “Milk of amnesia”

• Indication: *IV sedative/hypnotic* for *fast induction* (within 40 seconds) and maintenance of anesthesia and for sedation. Used to induce coma.
  
  – ↓ BP (vasodilation), bradycardia
  
  – ↓ respiration - requires intubation & mechanical ventilation

  – Otherwise, very fast recovery, minimal nausea, headache etc.

⚠️ Anaphylaxis, “Propofol Infusion Syndrome” (PrIS), cough, *apnea*, bradycardia, arrhythmias, hypotension, injection pain

ℹ️ Don’t drive

💦 Epilepsy, Elderly, debilitated

],& Synergy with other CNS depressants

!! Combo = Propofol + ketamine = Ketafol (for procedural sedation)
Propofol Infusion Syndrome (PrIS)

Constellation of metabolic & organ system failures characterized by:

- Severe metabolic acidosis, hyperkalemia, lipemia, rhabdomyolysis, hepatomegaly, cardiac and renal failure.

- Major risk factors include:
  - ↓ oxygen delivery to tissues;
  - Serious neurological injury and/or sepsis;
  - High dosages of:
    - vasoconstrictors, inotropes (catecholamines), steroids (glucocorticoids) and/or prolonged, high-dose infusions of propofol (> 5 mg/kg/h for > 48h)
  - The syndrome has also been reported following large-dose, short-term infusions during surgical anesthesia.

Beware of in trauma patients in a propofol induced coma
Parenteral General Anesthetics: Others/Adjuvants

- **Midazolam (Hypnovel, Versed) C-IV**
  - Benzodiazepine *for pre-op sedation/anxiolysis/amnesia; induction of anesthesia; sedation of ventilated patients*
  - Potent *amnesiac and sedative*
    - *Onset alone within 5 minutes, with a narcotic within 1.5 minutes*
  - Causes transient muscle movements

- **Respiratory depression/arrest**

---

- **Flumazemil (Romazicon)** antagonizes BZDs
Other Adjuvants

- Benzodiazepines
  - E.g., lorazepam, etc.
  - Anxiolytic, amnesia and sedation

- Opioids
  - Meperidine, Sufentanil, Alfentanil & Remifentanil
  - Potent analgesics

- Selective $\alpha_2$ adrenergic agonists
  - Dexmedetomidine
  - Short term sedation of critically ill patients

- NMJ blockers
  - Depolarizing - succinylcholine (shortest acting)
  - Non-depolarizing - pancuronium (preferred)

Chloral hydrate (Somnote) is a PO sedative hypnotic often used in kids

Reversed by Flumazenil

Reversed by Naloxone

NO Anti-AChE reversal!!

Reversed by Neostigmine

A Beale

PHRM 203 - Anesthetics
Inhaled General Anesthetics

• Absorption and excretion through lungs
  – Very rapid
  – Gases almost no metabolism; volatile liquids, lots of M

• *Minimal alveolar concentration* (MAC)
  – Measure of potency
  – \([\text{inhaled}]_{\text{drug}}\) needed to anesthetize 1/2 of patients

• Induction rate variables
  – Alveolar partial pressure of the anesthetic in air
  – Ventilation rate
  – Rate at which the patient’s partial pressure in the blood increases as the anesthetic is given

MAOIs and TCAs *increase* MAC

Other anesthetics, \(\alpha_2\) agonists, BZD, barbiturates *decrease* MAC
**General Anesthetics: Volatile liquids**

Inhalation only – administered by vaporization (vaporizer calibrated to specific agent)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset &amp; Recovery</th>
<th>Effects in Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other common agents:</td>
<td></td>
<td>• CV: ↓ contractility; cause peripheral vasoconstriction; sensitize the myocardium to catecholamines</td>
</tr>
<tr>
<td>Desflurane (smells)</td>
<td>Rapid (within minutes)</td>
<td>• ↓ cerebral blood flow ➔ ↑ intracranial pressure</td>
</tr>
<tr>
<td>Enflurane</td>
<td></td>
<td>• Apnea and bronchodilation</td>
</tr>
<tr>
<td>Halothane</td>
<td></td>
<td>• Potentiation of NMJB &amp; other GABA agonists</td>
</tr>
<tr>
<td>Isoflurane (Forane)</td>
<td></td>
<td>• ↓ uterine smooth muscle contractions</td>
</tr>
<tr>
<td>✪ Potent odor!</td>
<td></td>
<td>• Metabolized by CYP2E1, then conjugated</td>
</tr>
<tr>
<td>Sevoflurane (Ultane)</td>
<td></td>
<td><strong>Halogen may cause malignant hyperthermia</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>All cause PONV</strong></td>
</tr>
</tbody>
</table>
Isoflurane (Forane)

- MH history
- Hyperkalemia leading to arrhythmia (especially in kids), MH, ↑ intracranial pressure, PONV and shivering a problem
- Synergy with muscle relaxants (especially curare-based agents)
- ↓ intellect for 48 hrs (up to 6 days!), changes in mood

- Indicated for induction and maintenance of general anesthesia
- PUNGENT, MUSTY ODOR!
- Genetic susceptibility to malignant hyperthermia (MH)
- Methylphenidate (Ritalin) may trigger emergence from anesthesia
- Induction triggers cough, laryngospasm & breath holding – control with thiopental given 7-10 minutes before isoflurane

The halogenated volatile liquid anesthetics are usually given with $N_2O$
Sevoflurane (Ultane, Sojourn)

Indicated for in & outpatient induction and maintenance of general anesthesia

Genetic susceptibility to malignant hyperthermia (MH)

50-100% experience EEG Δ’s consistent with seizures

Sevoflurane degrades in the presence of soda lime to a nephrotoxin – avoid use in renal patients and maintain a flow rate of fresh gas (minimum of 1 L/minute)

MH history, kidney disease

Hyperkalemia leading to arrhythmias, MH, glycosuria & proteinuria, hypotension, seizures, PONV, coughing (rare), CNS agitation

Synergy with muscle relaxants (especially nondepolarizing agents)

↓ intellect for 48 hrs, changes in mood

A Beale
PHRM 203 - Anesthetics
### General Anesthetics: Gases

Adapted from: *Focus on Nursing Pharmacology, 4th Ed.*, by AM Karch. Lippincott, Williams & Wilkins. 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopropane (orange)</td>
<td>1-2 min</td>
<td>Rapid</td>
</tr>
<tr>
<td>Ethylene (red)</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Nitrous oxide, N₂O</td>
<td>1-2 min</td>
<td>Rapid</td>
</tr>
</tbody>
</table>

**Several issues:**

1. *liquid/gas under pressure and it can cause frostbite as its released;*
2. *nitrous oxide may cause suffocation; and*
3. *it is an OXIDIZER, so while it is non-flammable, it will SUPPORT (FUEL) A FIRE!*

---

*Nitrous oxide (N₂O) sounds like Nitric oxide (NO)*

*NO = INOmax, a gas used to treat respiratory failure in babies*
Gas Anesthetics: $\text{N}_2\text{O}$

- Inorganic gas (only one)
- Low solubility in blood
- Must be administered hyperbarically
  - MAC $\sim 105\%$ with high variability
- Analgesia with 20%, consciousness lost with 80% (some as low as 30%) - hypoxia a risk, so must be administered as an $\text{O}_2$ mix.
  - $\text{O}_2$ must be at least 19.5%, normal air = 21% $\text{O}_2$

Hypoxia & vomiting a problem with Nitrous oxide.
Gas Anesthetics: N$_2$O

- Risk of megaloblastic bone marrow changes and neuropathy similar to Vit B$_{12}$ deficiency
  - Megaloblastic anemia is characterized by many large (mega-), immature (blasts) RBCs (and no new ones)
  - Seen in dentists
  - Can be avoided by supplementing methionine

A Beale
Gas Anesthetics: N₂O

• Important use = adjuvant to \( \uparrow \) potency of anesthetic
• \( \downarrow \) MAC halothane from 0.75% to 0.3%
  – 60% reduction
• \( \downarrow \) MAC enflurane from 1.68% to 0.6%
  – 65% reduction
• \( \downarrow \) MAC isoflurane from 1.15% to 0.5%
  – ~60% reduction
• \( \downarrow \) MAC sevoflurane from ~3% to 1.2%
  – ~60% reduction

Remember: MAC = [drug] needed to stop 1/2 of patients from responding to surgical stimuli

And \( \downarrow \downarrow \) Costs!!