General Anesthetics

Pharmacology 604
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General Anesthesia - Characteristics

- Definition (G&G) - "Reversible depression of CNS function resulting in loss of response to and perception of all external stimuli."
  - Produce reversible "sleep"
  - Produce analgesia
  - Suppress reflexes
  - Produce muscle relaxation
  - Produce Amnesia
  - Do not suppress respiratory and cardiovascular function
  - Inexpensive and easy to administer

Balanced Anesthesia

- Ideal general anesthetic does not exist.
- Combinations of drugs to accomplish what one anesthetic can not do alone.
- Agents used for balanced anesthesia are -
  - Hypnotics
  - Neuromuscular blocking agents
  - Analgesics

COMBINATION OF DRUGS CAN LOWER DOSES OF EACH DRUG TO PRODUCE THE SAME OR GREATER EFFECT ON PATIENT

Four Stages of Anesthesia

- Stage I - analgesia
- Stage II - delirium
- Stage III - surgical anesthesia
- Stage IV - respiratory paralysis

Types of General Anesthetics

Extremely diverse group of chemicals which produce a similar endpoint

- Inhalant or volatile
- Injectable (intravenous)
Inhalational Anesthetics

- Administered as vapors or gases
- Special set of physical principles govern absorption, distribution, and elimination
- Partial pressure - proportional to the concentration of anesthetic in gas or tissue at equilibrium

Factors affecting MAC

Factors decreasing MAC
- Hypotension
- Anemia (PCV < 13%)
- Hypothermia
- Metabolic acidosis
- Extreme hypoxia (PaO2 < 38 mmHg)
- Age: old animal requires less anesthetic
- Premedication (opioids, sedatives, tranquilizers)
- Local anesthetics
- Pregnancy
- Hyperthyroidism
- Concurrent use of nitrous oxide

Factors increasing MAC
- Increasing body temperature
- Hypothyroidism
- Hypernatremia

Factors NOT affecting MAC
- Type of stimulation
- Duration of anesthesia
- Species
- Sex
- PaCO2 between range of 14-45 mmHg
- Metabolic alkalosis
- PaO2 between range of 38-500 mmHg
- Hypertension
- Potassium

Induction and Recovery

- The lower the blood:gas partition coefficient the faster the induction and recovery
  - The lower the solubility in blood, the faster the process of equilibration
  - Less drug has to be transferred via the lungs to the blood in order to achieve a given partial pressure
  - A single lungful of air containing a low-solubility agent will bring the partial pressure in the blood closer to that of the inspired air

- Recovery is the same
  - Low solubility in blood = fast induction and recovery
  - High solubility in blood = slower induction and recovery

MAC: Minimum Alveolar Concentration

- Potency measure
- 1 MAC is the concentration necessary to prevent responding in 50% of population

Solubility & Pharmacokinetics

- Solubility expressed as partition coefficients
  - a ratio of the concentration of the agent in two phases at equilibrium

  - Blood-gas partition coefficient
  - Solubility in blood
    - main factor that determines the rate of induction and recovery
  - Oil-gas partition coefficient
    - fat solubility
    - determines the potency of an anesthetic (as well as kinetics)

Anesthetic Properties

- Potency
- Blood Solubility
- Brain Solubility
**Nitrous Oxide**

- Relatively safe
  - Minimal effects on heart rate and blood pressure
  - Little effect on respiration
- Low blood solubility (quick recovery)
- MAC value is 105% - Needs other agents for surgical anesthesia
- Weak anesthetic, powerful analgesic

**Nitrous Oxide - Disadvantages**

- Cannot produce anesthesia without hypoxia
- Poor muscle relaxation
- Diffuses into closed spaces
- Inhibits vitamin B-12 metabolism
- Inhibits methionine synthetase (precursor to DNA synthesis)
- Abuse liability

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**Anesthetics - Halogenated ethers**

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**Halothane (Fluothane®)**

- Most potent inhalational anesthetic
  - MAC of 0.75%
- Very soluble in blood and adipose tissue
  - Prolonged emergence
- Inhibits sympathetic response to painful stimuli

**Halothane - Disadvantages**

- Decreases respiratory drive
- Depresses cardiovascular function
- Sensitizes myocardium - can lead to ventricular arrhythmias
- “Halothane Hepatitis”
- Malignant Hyperthermia

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**Enflurane (Ethrane®)**

- Stable, nonflammable liquid with pungent odor
- MAC 1.68%
- Cardiac effects
  - Depression and decreased systemic vascular resistance
  - Inhibits sympathetic baroreflex response
  - Sensitizes myocardium
- Decreases respiratory drive
- Metabolism one-tenth that of halothane
  - Releases fluoride ion - renal toxicity
- Epileptiform EEG patterns
**Isoflurane (Forane®)**

- Less soluble than halothane
- MAC of 1.30%
- Excellent muscle relaxant
- Depresses respiratory drive and ventilatory responses—less than enflurane
- Depresses cardiovascular system
  - Myocardial depressant—less than enflurane
  - Inhibits sympathetic baroreflex response—less than enflurane
  - Produces most significant reduction in systemic vascular resistance
- Sensitizes myocardium—less than enflurane

**Isoflurane Toxic Side Effects**

- Little metabolism (0.2%)—low potential of organotoxic metabolites
- No EEG activity like enflurane
- Bronchoirritating, laryngospasm

**Sevoflurane (Ultane®, Sevorane®) and Desflurane (Suprane®)**

- Low solubility in blood—produces rapid induction and emergence
- Minimal systemic effects—mild respiratory and cardiac suppression
- Few side effects
- Expensive

**Lipid-Based Theories of Anesthetic Action**

Hypothesized anesthetic effect was due to disruption of lipid bilayer of plasma membranes.

**Meyer Overton Correlation**

<table>
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<tr>
<th>Compound</th>
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**...however.....**

- Volume expansion by nonanesthetic compounds
- Correlation between fluidity and anesthetic levels only occurred at high concentrations.
- Small changes in temperature did produce significant fluidity changes without causing anesthesia while large changes in anesthetic concentration produced small changes in fluidity.
- Cut-off effect—M-O rule only holds up to a certain size
- Inhalant anesthetics show stereoselectivity in effects
Protein-based theories of Anesthetic Action

Anesthetics bind to hydrophobic/lipophilic sites on proteins.
- induce/prevent conformational change
- alter kinetics of conformational changes
- compete with ligands

Ok, so which receptors matter....

- GABA_A
- Glutamate (AMPA and NMDA)
- Glycine (strychnine-sensitive, in spinal cord and brainstem)
- Nicotinic ACh

Injectable anesthetics

- Advantages
  - minimal equipment
  - 'direct' CNS access
  - wide variety of agents, techniques
- Disadvantages
  - recovery dependent on uncontrollable factors
  - individual variation in drug response
  - potential for drug 'accumulation'

Barbiturates

- Phenobarbital
- Pentobarbital Sodium
- Thiopental Sodium
- Thiamylal Sodium
- Methohexital

Barbiturates - General

- Very alkaline - very irritating to tissues
- Depress polysynaptic responses in the CNS
- Effect on GABA receptors
  - Depress Reticular Activating System
  - Depress sympathetic nervous system
- Poor analgesics
- Excitement at low doses
- Low therapeutic index!

Cardiopulmonary Effects

- Arrhythmogenic!!!
  - Transient VPCs & ventricular bigeminy
- Transient, moderate decrease in blood pressure
- Decrease cardiac contractility
- Vascular effects variable, but in general cause mild vasodilatation
- Respiratory depressants
### Propofol

- **GABA_A positive modulator**
- Solubilized in an emulsion
- Rapid onset, short duration of action; rapid smooth recoveries w/o ‘hangover’
- Useful for induction &/or maintenance (by constant infusion)
- Mild to moderate hypotension, may produce bradyarrhythmias
- Respiratory depressant, may produce apnea

### Disadvantages

- Expensive
- Moderate hypotension, possible bradyarrhythmias, respiratory depression (apnea not uncommon)
- Poor analgesia (need high doses)
- Drug vehicle supports bacterial growth

### Etomidate

- **GABA_A positive modulator**
- Non-barbiturate ultrashort sedative/hypnotic
- Minimal cardiovascular effects
- Rapid onset/recovery
- Wide safety margin

### Dissociative Anesthetics

- Ketamine
- Tiletamine
- NMDA receptor channel blockers
- Produces amnesia, superficial analgesia, and catalepsy
- Dissociates the cortex from lower centers
- Both excitatory & depressant effects on EEG
- Actually has positive effects on CV measures and minimal respiratory depression

### Problems...

- Seizures
- Muscle rigidity
- Poor visceral analgesia
- Increased secretions
- Poor recoveries - delirium
- Increased myocardial work load

### Neuroleptanalgesia

- Combination of opioid + tranquilizer/sedative
- Produces state of light ‘anesthesia’
- Useful for debilitated or geriatric patients
- Eg fentanyl/diazepam; droperidol/fentanyl; oxymorphone/midazolam; etc...
Overview of mechanisms of action for general anesthetic.....

Ion Channels and Anesthesia

• GABA - primary anesthetic target
  - Act as modulators, not direct agonists
  - Increase current induced by low level GABA by >50%
  - Work by prolonging channel open-time
  - Inhalants, barbs, benzos, steroids, propofol

• Glycine - important for spinal cord and lower brainstem

• Glutamate - NMDA, AMPA & Kainate
  - Dissociative anesthetics
  - Relatively insensitive to inhalants (?) and barbiturates
  - nAChR - most simple anesthetics can stabilize desensitized form
  - Definitely involved in many inhalant effects
  - Increasing interest for role with other anesthetics

• Voltage gated ion channels -
  - Na⁺, K⁺, Ca²⁺
  - Do not appear to play a role in anesthesia

Potential Receptor Targets

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<th>Anesthetic</th>
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