Inhalational Agents

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Brief Mechanism of action

GABA-A receptor

A. No anesthetic

Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

B. In presence of inhaled anesthetic

Binding of GABA is enhanced by inhaled anesthetics, resulting in a greater entry of chloride ion.

Entry of Cl⁻ hypopolarizes cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Nitrous Oxide

Physical Properties:

- Non explosive, Nonflammable gas.
- Colorless, tasteless and essentially odorless gas at room temperature.
- The only inorganic anesthetic gas in clinical use.
- Weak Anesthetic good analgesic agent.
- Nitrous oxide, even at 80% concentration, doesn’t produce surgical level anaesthesia in most persons, so it must be used as an adjunct anaesthetic, along with other agents.
- Low blood solubility “0.47” blood/gas partition coefficient value.
- MAC value is 104% in adults.
- Excreted via lungs.
Nitrous Oxide Systemic Effects

• **Cardiovascular**:  
  - Depress myocardial contractility  
  - Arterial BP, CO, HR: unchanged or slightly ↑ due to stimulation of catecholamines  
  - Constriction of pulmonary vascular smooth muscle increase pulmonary vascular resistance  
    - Higher incidence of epinephrine-induced arrhythmia why?  
    - Because it has a tendency to stimulate the sympathetic nervous system

• **Respiratory**  
  - Respiratory rate: ↑  
  - Tidal volume: ↓  
  - Minute ventilation, resting arterial CO2: minimal change

• **Cerebral**  
  – CBF, cerebral blood volume, ICP: ↑  
  – Cerebral oxygen consumption (CMRO2): ↑
• **Neuromuscular**
  - Not provide significant muscle relaxation
  - At high concentration it can cause skeletal Muscle rigidity
  - Not a triggering agent of malignant hyperthermia
• **Renal**
  - Increase renal vascular resistance
  - Renal blood flow, glomerular filtration rate, U/O: ↓
• **Hepatic**
  - Hepatic blood flow: ↓
• **Gastrointestinal** :
  - Postoperative nausea and vomiting
Prolonged exposure to anesthetic concentrations of nitrous oxide can result in bone marrow depression (megaloblastic anemia) and even neurological deficiencies (peripheral neuropathies).
Nitrous Oxide (N2O) Second gas effect

Second gas effect: The ability of the large volume uptake of one gas (first gas) to accelerate the rate of rise of the alveolar partial pressure of a concurrently administered companion gas (second gas) is known as the second gas effect.
Nitrous Oxide (N₂O) Diffusion Hypoxia

What is diffusion hypoxia?

Diffusion hypoxia is a decrease in PO₂ usually observed as the patient is emerging from an inhalational anesthetic where nitrous oxide (N₂O) was a component. The rapid outpouring of insoluble N₂O can displace alveolar oxygen, resulting in hypoxia. All patients should receive supplemental O₂ at the end of an anesthetic and during the immediate recovery period.
Nitrous Oxide (N2O) Effect on closed gas spaces

Nitrous oxide can diffuse (20-30) times faster into closed spaces than it can be removed, resulting in expansion of pneumothorax, bowel gas, or air embolism or in an increase in pressure within noncompliant cavities such as the cranium or middle ear.
• Contraindications

- Venous or arterial air embolism
- Pneumothorax
- Acute intestinal obstruction with bowel distention
- Pulmonary air cysts
Halothane

Physical Properties:
- Halogen substituted ethane
- Non pungent Volatile liquid easily vaporized, stable, and nonflammable.
- Most potent inhalational anesthetic, but not a good analgesic and it’s muscle relaxation effect is moderate.
- Efficacious in depressing consciousness.
- Very soluble in blood and adipose “2.4” blood/gas partition coefficient.
- **MAC of 0.75%**
- The induction dose varies from patient to patient 0.5-3%. The maintenance dose varies from 0.5 to 1.5%
- Halothane may be administered with either oxygen or a mixture of oxygen and nitrous oxide.
Halothane Systemic Effects:

• **Cardiovascular:**
  - Direct myocardial depression---> dose-dependent reduction of arterial BP
  - Coronary artery vasodilator, but coronary blood flow↓ due to systemic BP↓
  - Hypotension inhibits baroreceptors in aortic arch and carotid bifurcation --> vagal stimulation↓ - >compensatory rise in HR (Halothane blunt this reflex result in bradycardia).
  - Sensitizes the heart to the arrhythmogenic effects of epinephrine, so doses of epinephrine above 1.5 mcg/kg should be avoided.
  - Systemic vascular resistance: unchanged.

• **Respiratory:**
  - Rapid, shallow breathing
  - Alveolar ventilation: ↓”because the ↑RR isn’t enough to counter the ↓tidal volume”
  - Resting PaCO2: ↑ “Apneic Threshold” the highest PaCO2 at which a patient remains apneic.
  - Hypoxic drive: severely depressed even by low concentration of Halothane.
  - A potent bronchodilator, reverses asthma-induced bronchospasm.
  - Depress clearance of mucus promoting postoperative hypoxia and atelectasis.
Halothane Systemic Effects:

• Cerebral :
  - Dilating cerebral vessels -> cerebral vascular resistance↓ → CBF ↑
  - Blunt auto regulation (the maintenance of constant CBF during changes in arterial BP).
  - ICP: ↑ prevented by hyperventilation prior to administration of halothane.
    - Cerebral activity↓: leading to ↓Metabolic oxygen requirement.
• Neuromuscular :
  - Relaxes skeletal muscle.
    - A triggering agent of malignant hyperthermia
      1/60,000 cases (autosomal dominant inheritance)
  
  Classic: rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, hyperkalemia, DIC

  Diagnosis -- previous symptoms, increase CO2, rise in CPK levels, myoglobinuria

  Treatment -- early detection, hyperventilate, IV dantrolene (2.5 mg/kg), ice packs/cooling blankets, Lasix/mannitol/ fluids.

  ICU monitoring
• **Renal**:  
  - Renal blood flow, GFR, U/O: ↓  
  - Because the reduction in renal blood flow is greater than the reduction in glomerular filtration rate, the filtration fraction is increased. Preoperative hydration limits these changes.

• **Hepatic**:  
  - Hepatic blood flow: ↓  
  - "Halothane Hepatitis" -- 1/35,000 cases (rare)  
    Patients exposed to multiple halothane anesthetics at short intervals, middle-aged obese women, and persons with a familial predisposition to halothane toxicity or a personal history of toxicity are considered to be at increased risk. Present with fever, jaundice, increased ALT AST, hepatic necrosis.

• **Biotransformation & toxicity**:  
  - Oxidized in liver by cytochrome P-450 to trifluoroacetic acid.
• **Contraindications:**

- Unexplained liver dysfunction following previous exposure.
- No evidence associating halothane with worsening of preexisting liver disease.
- Intracranial mass lesions because of the possibility of intracranial hypertension secondary to increased cerebral blood volume and blood flow.
- Hypovolemic patients & patients with severe LT ventricular dysfunction may not tolerate halothane’s negative inotropic effects.

• **Drug interactions:**

- Myocardial depression is exacerbation by β-blockers and CCB.
- With aminophylline → serious ventricular arrhythmia.
Halogenated Organic Compounds

- **Isoflurane and sevoflurane**, are the most commonly used agents in this class
  - Others include??
  - Desflurane, Halothane, and Enflurane, but these are not commonly used
- Pungent & Liquid at room temperature
- Stored in a vaporizer on an anesthetic machine
- Vaporized in oxygen that flows through the vaporizer
Isoflurane

- **Physical properties:**
  - Nonflammable
  - **MAC of 1.15 %**
  - Haloginated methyl ethyl ether
  - A chemical isomer of enflurane
  - Often another medication is used to start anesthesia due to airway irritation with isoflurane.
• **Mechanism of action:**
Isoflurane likely binds to GABA, glutamate and glycine receptors, but has different effects on each receptor.

Isoflurane acts as a positive allosteric modulator of the GABA$\text{A}_\Delta$ receptor. It potentiates glycine receptor activity, which decreases motor function. It inhibits receptor activity in the NMDA glutamate receptor subtypes.

• **Isoflurane Systemic Effects:**
  • **Cardiovascular**
    - Minimal cardiac depression
    - HR: ↑ due to partial preservation of carotid baro reflex so maintain CO
    - Systemic vascular resistance↓: ↓BP
    - Dilates coronary arteries
    - Sensitizes myocardium to catecholamine -- less than halothane or enflurane
• **Respiratory**
  - Respiratory depression & decreased minute ventilation but tachypnea less pronounced.
  - Blunt the normal ventilatory response to hypoxia and hypercapnia.
  - Irritate upper airway reflex.
  - A good bronchodilator not potent as halothane.

• **Neuromuscular**:
  - Isoflurane relaxes skeletal muscle.

• **Renal**:
  - Isoflurane decreases renal blood flow, glomerular filtration rate, and urinary output.

• **Hepatic**:
  - Total hepatic blood flow: \( \downarrow \)
  - Liver function tests are usually not affected.
• **Contraindications**:
  Isoflurane presents no unique contraindications. Patients with severe hypovolemia may not tolerate its vasodilating effects. It can trigger malignant hyperthermia.

• **Drug Interactions**:
  Epinephrine can be safely administered in doses up to 4.5 mcg/kg. Non depolarizing NMBAs are potentiated by Isoflurane.
Sevoflurane

Physical Properties:
-Halogenated ether
-Non flammable.
-Non irritant & has sweet odor even at high concentrations, making this the agent of choice for inhalational induction.
-Low blood solubility “0.65” blood/gas partition coefficient (fast in induction & recovery)
-fastest for induction, inhalation induction with 4-8% Sevoflurane in a 50% mixture of nitrous oxide and oxygen can be achieved within 1 min
-MAC 2%.
Sevoflurane Systemic effects

- **Cardiovascular**
  - Mildly depress myocardial contractility
  - Systemic vascular resistance, arterial BP: ↓
  - CO: not maintained well due to little rise in HR
  - Prolong QT interval
- **Respiratory**
  - Depress respiration
  - Reverse bronchospasm
- **Hepatic**
  - Portal vein blood flow: ↓
  - Hepatic artery blood flow: ↑
• **Cerebral**
  - CBF, ICP: slight ↑
  - Cerebral metabolic oxygen requirement: ↓
• **Neuromuscular**
  - Adequate muscle relaxation for intubation of children
• **Renal**
  - Renal blood flow: slightly ↓
  - Associated with impaired renal tubule function
• **Contraindications**
  - Severe hypovolemia
  - Susceptibility to malignant hyperthermia & intracranial hypertension

• **Drug interactions**
  - Potentiate NMBAs
  - Not sensitize the heart to catecholamine-induced arrhythmias
Desflurane

MAC = 6 %
Enflurane

MAC = 1.68%

Potent cardiovascular depressant
Thank You