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INHALATIONAL ANESTHETICS

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- ***Anesthesia*** defined as the abolition of sensation
- ***Analgesia*** defined as the abolition of pain

- "Triad of General Anesthesia"
  - need for unconsciousness
  - need for analgesia
  - Need for amnesia
  - (±) need for muscle relaxation

Signs and Stages of Anesthesia

Sedation. *Mild CNS depression*. Suitable for surgical procedures not requiring muscle relaxation. Most anesthetics do not produce analgesia.

Delirium: An excited state resulting from *cortical motor depression*. This can be avoided with rapidly acting, potent anesthetics. This stage extends from the loss of consciousness in stage 1 to surgical anesthesia in stage 3.

Surgical Anesthesia: Further subdivided into stages representative of increasing *muscle relaxation*, the final stage is disappearance of muscle tone.

Deep anesthesia and Respiratory paralysis: Generally not desirable.

Inhalational Anesthetic Agents

- Inhalational anesthesia refers to the delivery of *gases or vapors* from the respiratory system to produce or maintain anesthesia

- Exposure to the pulmonary circulation allows a more rapid appearance in arterial blood than intravenous administration

Advantages of inhalational anesthesia

- Completely painless induction
- No IV (intravenous) access needed
- Rapid appearance of drug in arterial blood
- Safe: as long as patient is breathing satisfactorily, elimination of agent and emergence from anesthesia is essentially guaranteed.

1840, William Morton publically administered ***ether***

1847, James Simpson introduced ***chloroform***

It was more potent but could have severe side effects such as sudden death and late onset severe liver damage

1877, introduction of ***local anesthesia***

1920's ***intravenous*** induction agents were introduced

1940's ***Muscle relaxants*** were introduced

Minimum Alveolar Concentration

- Minimal alveolar concentration of inhalational agent that prevent movement in 50% of the patients in response to surgical stimulation (skin incision)

- Equivalent to ED_{50}

Minimum Alveolar Concentration

- **The rationale for this measure of anesthetic potency is,**
  - a. alveolar concentration can be *easily measured*
  - b. near *equilibrium*, alveolar and brain tensions are virtually equal
  - c. the high cerebral blood flow produces *rapid equilibration*
- **Factors which support the use of this measure are,**
  - a. MAC is invariant with a variety of noxious stimuli
  - b. individual variability is small
  - c. sex, height, weight & anaesthetic duration do not alter MAC
  - d. doses of anaesthetics in MAC's are additive

Factors affecting MAC

PHYSIOLOGIC & PHARMACOLOGIC FACTORS AFFECTING MAC

Increase in MAC:-

- Hyperthermia
- Hypernatraemia
- Drug induced elevation of CNS catecholamine stores
- Chronic alcohol abuse & chronic opioid abuse
- Increases in ambient pressure (experimental)
- Cyclosporine
- Excess pheomelanin production(red hair)

Decrease in MAC:-

- Hypothermia & Hyperthermia (if >42◦ C)
- Hyponatraemia
- Drug induced decrease in CNS catecholamine level
- Increasing age (6% decrease/decade)
- Preoperative medication
- Hypoxaemia (PaO_2< 38mmHg)
- Hypotension(<40 mm hg- MAP)
- Anaemia (Haematocrit<10%)
- Pregnancy (progesterone)
- Postpartum(returns to normal in 24-72 hrs)
- CNS depressant drugs – Opioids,Benzodiazepines TCA's etc.
- other drugs–lithium, Lidocaine,Magnesium
- acute alcohol abuse
- Cardiopulmonary bypass

Ideal Characteristics

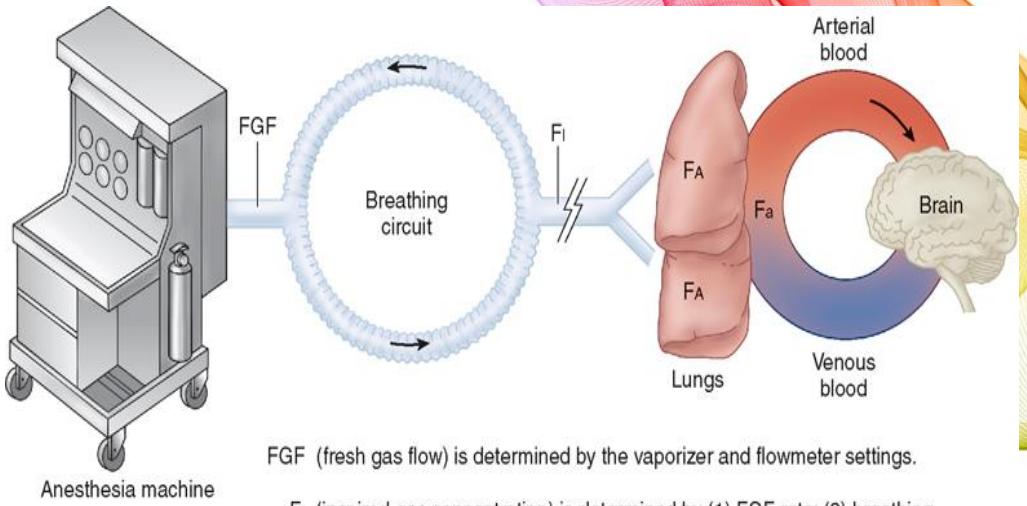
1. Be pleasant to inhale, permitting a smooth induction and emergence.
2. Be potent to allow the concomitant administration of high oxygen.
3. Rapid induction and emergence (low solubility).
4. Be easy to administer and analyze
5. Be easily and cheaply prepared in pure form.
6. Be stable in storage and with soda-lime, not flammable, not metabolized.
7. Act at specific CNS sites to cause unconsciousness.
8. No CV or respiratory effects, non-toxic to organ systems.
9. Provide postop pain relief.

Uptake and Distribution

The depth of general anesthesia depends on the partial pressure (or gas fraction) exerted by the inhalational agent in the patient brain (b).

This brain partial pressure depends on arterial (a) blood partial pressure which depends on alveolar (A) partial pressure which depends on partial pressure of agent in the inspired gas (I):

$p_I \rightarrow p_A \rightarrow p_a \rightarrow p_b$



FGF (fresh gas flow) is determined by the vaporizer and flowmeter settings.

FI (inspired gas concentration) is determined by (1) FGF rate; (2) breathing-circuit volume; and (3) circuit absorption.

FA (aveolar gas concentration) is determined by (1) uptake (uptake = λb/g x C(A-V) x Q); (2) ventilation; and (3) the concentration effect and second gas effect:
a) concentrating effect
b) augmented inflow effect

Fa (arterial gas concentration) is affected by ventilation/perfusion mismatching.

Source: Butterworth JF, Mackey DC, Wasnick JD: *Morgan & Mikhail's Clinical Anesthesiology*, 5th Edition: www.accessmedicine.com

Halothane

- Halogen substituted ethane
- Volatile liquid easily vaporized, stable, and nonflammable
- Most potent inhalational anesthetic
- MAC of 0.75%
- Efficacious in depressing consciousness
- Very soluble in blood and adipose
- Prolonged emergence

Halothane

Halothane Systemic Effects

Cardiovascular

- Direct myocardial depression → dose-dependent reduction of arterial BP
- Systemic vascular resistance: unchanged
- Coronary artery vasodilator, but coronary blood flow ↓ due to systemic BP ↓
- Blunt the reflex: hypotension inhibits baroreceptors in aortic arch and carotid bifurcation → vagal stimulation ↓ → compensatory rise in HR
- Sensitzes the heart to the arrhythmogenic effects of epinephrine

Halothane

Halothane Systemic Effects

Respiratory

- Rapid, shallow breathing
- Alveolar ventilation: ↓
- Resting PaCO2: ↑
- Hypoxic drive: severely depressed
- A potent bronchodilator, reverses asthma-induced bronchospasm
- Depress clearance of mucus → promoting postoperative hypoxia and atelectasis

Halothane

Halothane Systemic Effects

Cerebral

- Dilating cerebral vessels → cerebral vascular resistance ↓ → CBF ↑
- Blunt autoregulation (the maintenance of constant CBF during changes in arterial BP)
- ICP: ↑, prevented by hyperventilation prior to administration of halothane
- Metabolic oxygen requirement: ↓

Neuromuscular

- Relaxes skeletal muscle
- A triggering agent of malignant hyperthermia

Halothane

Halothane Systemic Effects

Renal

- Renal blood flow, GFR, U/O: ↓
- Part of this can be explained by a fall in arterial BP and CO, preoperative hydration limits these changes

Hepatic

- Hepatic blood flow: ↓

Halothane

Halothane Side Effects

Halothane Hepatitis" -- 1/35,000 cases

- oxidized in liver by cytochrome P-450 2EI to trifluroacetic acid
- fever, jaundice, hepatic necrosis, death
- immunologically mediated assault
- exposure dependent

Halothane

Halothane Side Effects

Malignant Hyperthermia-- 1/60,000

- **Classic** -- rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, hyperkalemia, DIC
- **physiology**--hypermetabolic state by inhibition of calcium reuptake in sarcoplasmic reticulum
- **Diagnosis** -- previous symptoms, increase CO2, rise in CPK levels, myoglobinuria
- *autosomal dominant* inheritance
- **Treatment** -- early detection, d/c agents, hyperventilate, bicarb, IV dantrolene (2.5 mg/kg), ice packs/cooling blankets, lasix/mannitol/ fluids.
- **ICU monitoring**

Halothane

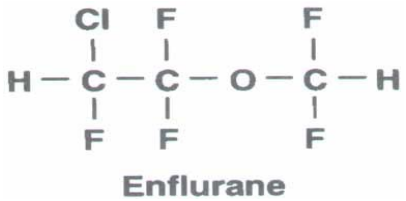
Contraindications

- Unexplained liver dysfunction following previous exposure
- Intracranial mass lesion, hypovolemic, severe cardiac disease…

Drug interactions

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

Enflurane



- Developed in 1963 by Terrell, released for use in 1972
- Stable, nonflammable liquid
- MAC 1.68%
- Haloginated methyl ethyl ether.

Enflurane

Enflurane Systemic Effects

Cardiovascular:

- Inhibits sympathetic baroreflex response
- Sensitizes myocardium to effects of exogenous catecholamines – arrhythmias
- Potent inotropic and chronotropic depressant and decreases systemic vascular resistance-- lowers blood pressure and conduction dramatically

Enflurane

Enflurane Systemic Effects

Respiratory

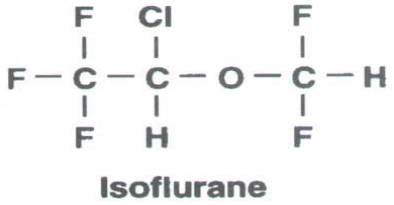
- drive is greatly depressed -- central and peripheral responses
- increases dead space
- widens A-a gradient
- produces hypercarbia in spontaneously breathing patient
- bronchodilator

Enflurane

Enflurane Side Effects

- Metabolism one-tenth that of halothane-- does not release quantity of hepatotoxic metabolites
- Metabolism releases fluoride ion-- renal toxicity
- Epileptiform EEG patterns

Isoflurane



Isoflurane

- Nonflammable,pungent
- MAC of 1.20 %
- Haloginated methyl ethyl ether
- A chemical isomer of enflurane

Isoflurane

Isoflurane Systemic Effects

Cardiovascular

- Minimal cardiac depression
- Systemic vascular resistance: ↓(Produces most significant reduction in systemic vascular resistance) → BP: ↓
- Dilates coronary arteries → coronary steal syndrome or drop in perfusion pressure → regional myocardial ischemia → avoided in patients with CAD
- Sensitizes myocardium to catecholamines -- less than halothane or enflurane

Isoflurane

Isoflurane Systemic Effects

Respiratory

- Respiratory depression, minute ventilation: ↓
- Blunt the normal ventilatory response to hypoxia and hypercapnia
- Irritate upper airway reflex
- A good bronchodilator

Cerebral

- CBF, ICP: ↑, reversed by hyperventilation
- Cerebral metabolic oxygen requirement: ↓

Neuromuscular

- Relaxes skeletal muscle

Isoflurane

Isoflurane Systemic Effects

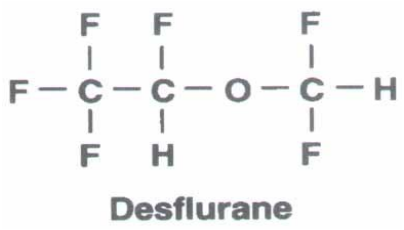
Renal

- Renal blood flow, GFR, U/O: ↓

Hepatic

- Total hepatic blood flow: ↓

Desflurane



- Structure is similar to isoflurane
- High vapor pressure
- requires special vaporizer
- Low solubility → *ultrashort duration of action*
- Moderate potency
- MAC 6%

Desflurane

Desflurane systemic effects

Cardiovascular

- Systemic vascular resistance: ↓ → BP: ↓
- CO: unchanged or slightly depressed
- Rapid increases in concentration lead to transient elevation in HR, BP, catecholamine levels

Desflurane

Desflurane systemic effects

Respiratory

- Tidal volume: ↓, respiratory rate: ↑
- Alveolar ventilation: ↓, resting PaCO2: ↑
- Depress the ventilatory response to ↑PaCO2
- Pungency and airway irritation

Cerebral

- Vasodilate cerebral vasculature → CBF, ICP: ↑, lowered by hyperventilation
- Cerebral metabolic rate of oxygen: ↓

Desflurane

Desflurane systemic effects

Neuromuscular

- Dose-dependent decrease in the response to train-of-four and tetanic peripheral nerve stimulation

Renal

- No evidence of any nephrotoxic effects

Hepatic

- No evidence of hepatic injury

Desflurane

Desflurane side effects

Degraded by desiccated CO2 absorbent into **carbon monoxide**

Desflurane

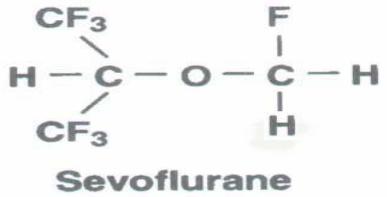
Contraindications

- Severe hypovolemia, malignant hyperthermia, intracranial hypertension

Drug interactions

- Potentiate nondepolarizing NMBAs

Sevoflurane



Sevoflurane

- Nonpungency
- Rapid increase in alveolar anesthetic concentration
- Smooth and rapid inhalation inductions in pediatric and adult patients
- MAC 2%

Sevoflurane

Sevoflurane systemic effects

Cardiovascular

- Mildly depress myocardial contractility
- Systemic vascular resistance, arterial BP: ↓
- CO: not maintained well due to little rise in HR

Respiratory

- Depress respiration
- Reverse bronchospasm

Sevoflurane

Sevoflurane systemic effects

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

Hepatic

- Portal vein blood flow: ↓

Sevoflurane

Sevoflurane side effects

Biotransformation & toxicity

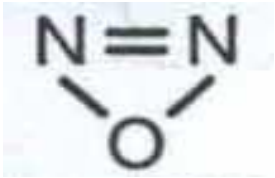
- Liver microsomal enzyme P-450
- Degraded by alkali (barium hydroxide lime, soda lime), producing nephrotoxic end products **(compound A)**

Sevoflurane

Contraindications

- Severe hypovolemia, susceptibility to malignant hyperthermia, intracranial hypertension

Nitrous Oxide



- The only inorganic anesthetic gas in clinical use
- Characterized by inert nature with minimal metabolism
- Colorless, odorless, tasteless, and does not burn
- Week Anesthetic good analgesic agent
- Major difference is low potency
- MAC value is 104%
- Needs other agents for surgical anesthesia
- Low blood solubility

Nitrous Oxide

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
- Peripheral vascular resistance: not altered

Nitrous Oxide

Nitrous Oxide Systemic Effects

Respiratory

- Respiratory rate: ↑
- Tidal volume: ↓
- Minute ventilation, resting arterial CO2: minimal change
- Hypoxic drive (ventilatory response to arterial hypoxia): ↓

Cerebral

- CBF, cerebral blood volume, ICP: ↑
- Cerebral oxygen consumption (CMRO2): ↑

Nitrous Oxide

Nitrous Oxide Systemic Effects

Neuromuscular

- Not provide significant muscle relaxation
- 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

Nitrous Oxide

Nitrous Oxide Side Effects

- Beginning of case: second gas effect
- Diffusion into closed spaces
- Inhibits vitamin B-12 metabolism

Nitrous Oxide

Contraindications

- N_2O diffuse into the cavity more rapidly than air (principally N_2) diffuse out

  Pneumothorax, air embolism, acute intestinal obstruction, intracranial air, pulmonary air cysts, intraocular air bubbles, tympanic membrane grafting
- Avoided in pulmonary hypertension

Xenon

- Nonexplosive, nonpungent, odorless and chemically inert
- No metabolism and low toxicity
- High cost
- MAC 71%
- It has some analgesic effect.
- Reduces anesthesia-emergent nausea and vomiting
- Very close to the ‘ideal agent’
- Minimal haemodynamic effects.
- Seems not to trigger malignant hyperthermia.

MAC

Halothane	0.75%
Enflurane	1.6%
Isoflurane	1.2%
Desflurane	6%
Sevoflurane	2%
Nitrous Oxide	104%
Xenon	71%

Respiratory Effects

Type of breathing

- Rapid shallow breathing
- Decrease minute ventilation
- Increase PaCO2

Hypoxic drive

- 0.1 MAC produce 50% depression
- 1.1 MAC produce 100% depression

Airway resistance

- They cause bronchodilation
- They can cause airway irritation

Cardiovascular Effects

- All causedecrease in BP (ex. N2O)
- Isoflurane and desflurane cause increased heart rate which may mask depression

Systemic vascular resistance

- Isoflurane and desflurane cause most decrease
- Halothane and nitrous oxide do not change
- Steal phenomena

Cardiovascular Effects

MAP

- N_2O cause no or modest increase
- Halothane cause decrease by cardiac depression
- Others causes decrease by causing decrease SVR

HR

- Halothane does not cause tachycardia.
- Others increase HR

CNS Effects

CBF:

- >0.6 MAC in normocapnic pt. produce cerebral vasodilation and results in dose dependent increase in CBF.

O2 requirements:

- All decrease (except N2O)

ICP

- All increase

Renal Effects

- All decrease arterial pressure
- They cause a dose related *decrease in renal blood flow, glomerular filtration rate and urine output.*
- RBF and GFR will be maintained until threshold of autoregulation
- Enflurane …… nephrotoxic

Hepatic effects

Circulation

- Hepatic blood flow is maintained or decreased

Hepatic function

- Transient increase in liver enzymes

Skeletal muscle effects

NMJ

- They cause dose dependent potentiation of NMBD (except for N2O)

Malignant hyperthermia

Obstetric effects

- Produce dose dependent decrease in uterine contractility and blood flow
- may cause uterine atony and PPH
- They rapidly cross the placenta and reach the fetus