General anesthesia

- General anesthesia was absent until the mid-1800's
- Diethylether was the first general anesthesia used for surgery
- General Anesthetics now divided into two classes
  - (Inhaled (usually halogenated)
  - Intravenous (anesthetics or induction agents)

Anesthesia

The administration of drugs that alleviate pain or other sensation and movement

Local

Effects a specific region of the PNS

General

Effects CNS

General anesthesia is a state of reversible loss of consciousness for the purpose of carrying out surgery.

General Anesthetics –
Pharmacological Effects

- **Anesthesia involves three main changes:**
  - **Analgesia** — ***loss of response to pain***
  - **Amnesia** — ***loss of memory***
  - **Immobility** – ***loss of motor reflexes***
    - Loss of Consciousness
    - Skeletal muscle relaxation

General Anaesthetics

- Absence of sensation associated with a reversible loss of consciousness
- Most sensitive site of action for general aneasthetics is the reticular activating system of the brainstem (RAS)
- Anesthetic dose: does not cause depression of cardiac, vasomotor or respiratory centers
- Has a small margin of safety

Inhaled Anesthetics

- Inhaled anesthetics
  - Nitrous oxide
  - Halothane
  - Enflurane
  - Isoflurane
  - Desflurane

Intravenous Anesthetics

- Intravenous anesthetics
  - *Barbiturates*
    - Thiopental & Methohexital
  - *Opioids*
    - Alfentanil, Meperidine, Fentanyl, Sufentanil (agonists)
    - Naloxone (antagonist)
  - *Benzodiazepine*
    - Diazepam, Midazolam
    - Flumazenil (antagonist)

Intravenous Anesthetics

- Miscellaneous Agents
  - ***Etomidate*** - nonbarbiturate hypnotic agent without analgesic properties
  - ***Droperidol*** - Neuroleptic (butyrophenone similar to Haloperidol) - combined with Fentanyl
  - ***Ketamine*** - dissociative anesthetic
  - ***Propofol*** - New (1989) and unrelated to other intravenous anesthetic agents
  - ***Alpha2 adrenergic agonists*** - Clonidine & others

General Uses of IV Anesthetics

- Primary Use = induction of general anesthesia
  - Supplement general anesthesia
  - maintain general anesthesia
  - provide sedation
  - control Blood Pressure

Intravenous agents

- Mechanism of action
  - Act at cell surface receptors
    - Barbiturates and benzodiazepine act at GABA-A receptors to increase Cl- influx
    - Opioids act on μ and other subtypes
    - Ketamine antagonizes PCP site on NMDA receptors (prevent excitation)
- Pharmacokinetics
  - Rapid induction = shorter acting
  - Duration of effect proportional to redistribution from brain to other tissue

Barbiturates: Thiopentone (PENTOTHAL)

- Ultra-short acting hypnotic with no analgesic action
- Has rapid onset of action and recovery
- Uses
  - most common induction drug,
  - Block BP increase & provide brain protection against increased intracranial pressure
- M.O.A.= potentiates GABA, decrease glutamate activity, increase chloride ion conductance

Adverse reactions: decreased myocardial and respiratory activity

Etomidate (AMIDATE)

- Activate GABA receptors
- Uses
  - Induction of anesthesia in hemodynamically unstable patients
  - Minimum side effects on CV or respiration.
- Side effects
  - Myoclonus
  - Inhibits 11-β-hydroxylase (key enzyme for steroid production). May cause death if used for long periods, but not after single injection
  - Post-op nausea and vomiting

Ketamine (KETALAR)

- Uses- Induction of anesthesia
  - in children (any route)
  - in severely hypovolemic patients
  - Supplement sedation during painful procedures
- Contraindications
  - Increased intracranial pressure
  - Ischemic heart disease
  - Psychological disorders
- Effects
  - Analgesic with dissociative anesth. properties
  - Dreaming & emergence reactions (< in children)

Propofol (DIPRIVAN)

- **Uses**
  - **Induction and maintenance of anesthesia with sedation and nausea reduction**
- **Contraindications**
  - **Cardiovascular instability**
- **Effects**
  - **Hypnosis w/o analgesia (similar to barbiturates except for slightly more CV depression)**
  - **Antiemetic**
  - **Fast acting/short duration. Fewer peripheral side effects compared to barbiturates**

Opiates

- **Potent analgesics (act at many subtypes)**
  - **Fentanyl (SUBLIMAZE)-Potency 50-100X >Morph**
  - **Alfentanil (ALFENTA)-Potency 25-30X > Morph**
  - **Sufentanil (SUFENTA)-Potency 5-10X >Fentanyl**
  - **Meperidine (DEMEROL)**
- **Uses**
  - **Supplementation of general anesthesia or analgesia**
- **Effects**
  - **respiratory depression**
  - **nausea and vomiting**
  - **muscle rigidity**

IV agent Toxicity & Side Effects Summary

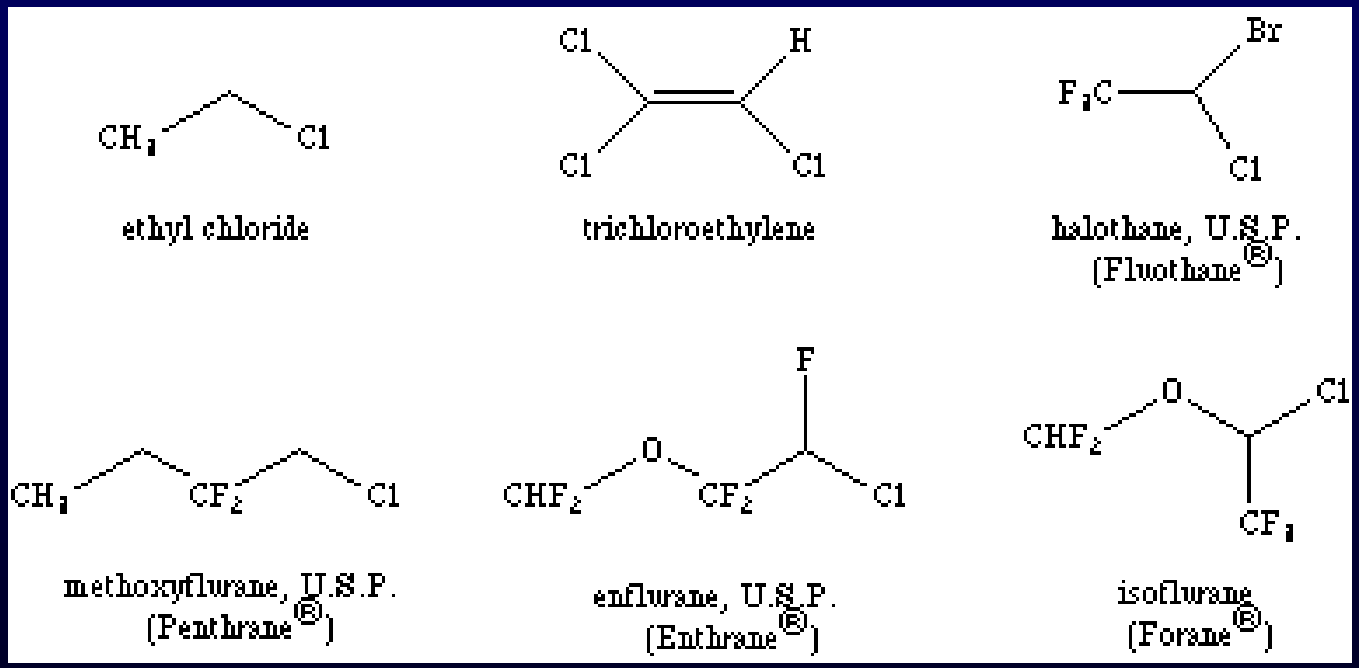
- Depression of respiratory drive
  - Opioid induction agents
- Depression of cardiovascular drive
- Muscle rigidity
  - Opioids
  - Ketamine

IV agent Toxicity and Side Effects Summary

- Hallucinations
  - Ketamine can elicit “bad dreams” and emergence delirium
- Steriodogensis inhibition
  - Occurs with etomidate which suppresses the adrenal cortex 4-8 hours and corticosteroid response to stress
- Reduction in Pain threshold
  - Thiopental

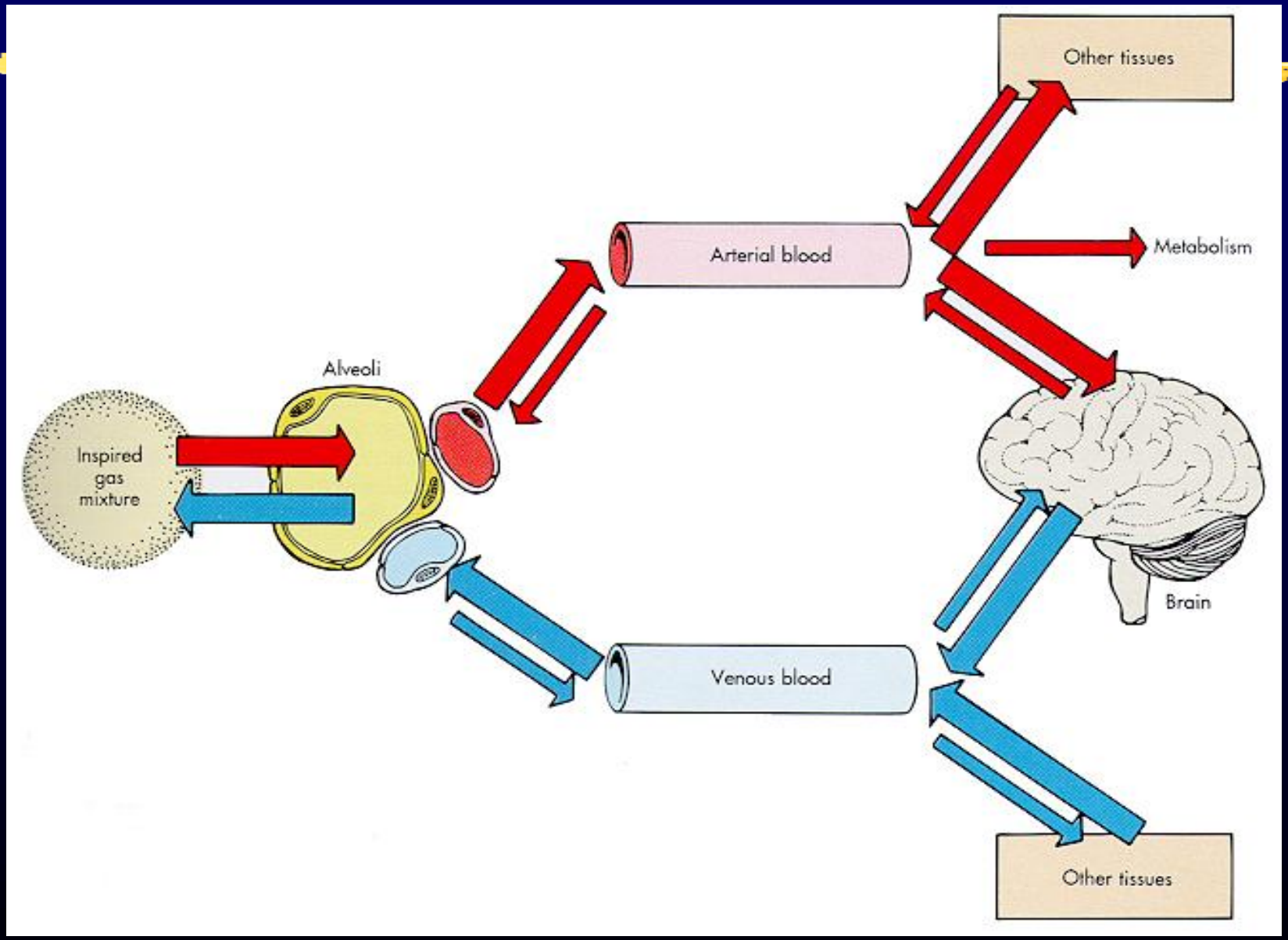
Inhaled Anesthetics

- Types



  - Halogenated compounds
    - Contain Fluorine and/or bromide
    - Simple, small molecules

Pathway for General Anesthetic Action



MAC(minimal alveolar concentration)

- MAC of anaesthetic measures potency of anaesthetic
- Defined as the concentration of anesthetic that prevents movement induced by a painful stimulus in 50 % of subjects.

Mechanism of Action

- Potency correlated with lipid solubility
  - Olive oil:gas partition coefficient
    - The greater the number, the more potent the anesthetic
    - Methoxyflurane>halothane>isoflurane etc.

TABLE: Pharmacological characteristics of Inhaled Anesthetics

AGENT	*MAC*	*OIL:GAS*	*BLOOD:GAS*	*DOSE METAB.(%)*
Nitrous Oxide	105	1.4	0.47	~0
desflurane	7.0	19	0.42	0.5
sevoflurane	2.0	53	0.63	3
diethyl ether	1.9	65	12	0
enflurane	1.7	98	1.9	3
isoflurane	1.2	98	1.4	0.5
halothane	0.75	225	2.3	15
methoxyflurane	0.16	825	13	60

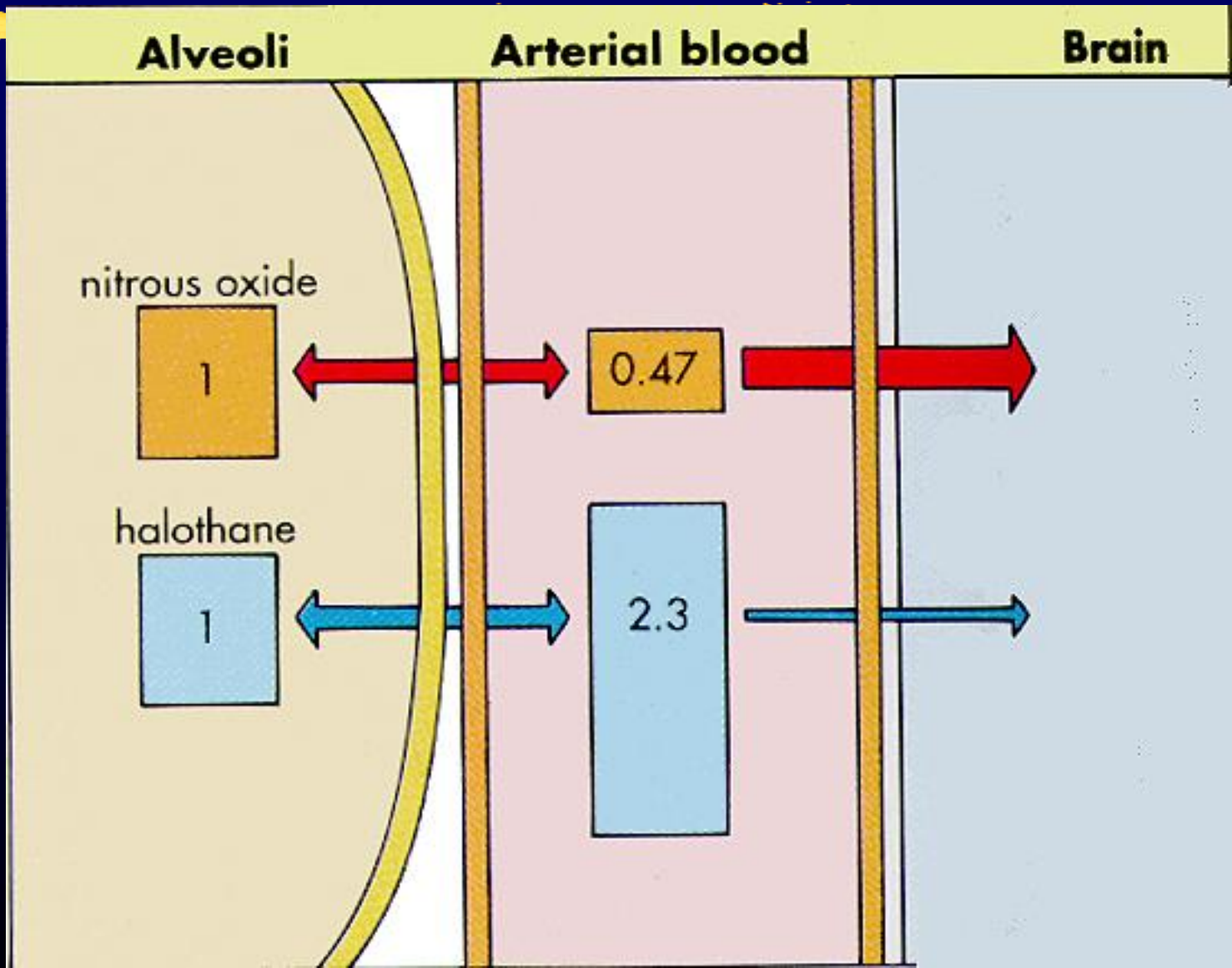
Theories for Mechanism of Action

- Theory #1
  - Gas movement into lipid membrane disrupting ion channels and action potential propagation
    - Increase Atms pressure with reverse effects
- Theory #2
  - Binding theory = anesthetics bind to hydrophobic portion of the ion channel
- Theory #3
  - Neuromodulator theory = bind to cell-surface receptors.
    - increased Cl- flux (possible GABA mediation)

Pharmacokinetics of Inhaled Anesthetics

- Factors influencing the effects of inhaled anesthetics
  - Amount that reaches the brain
    - Indicated by oil:gas ratio (lipid solubility)
  - Partial pressure of anesthetic
    - 5% anesthetic = 38 mmHg (10%=76 mmHg)
  - Solubility of gas into blood
    - The lower the blood:gas ratio, the more anesthetic will arrive at the brain
  - Cardiac Output
    - Increased CO = greater Induction time

Rate of Entry into the Brain: Influence of Blood and Lipid Solubility



General Actions of Inhaled Anesthetics

- Respiration
  - Depressed respiration and response to CO_2
- Kidney
  - Depression of renal blood flow and urine output
- Muscle
  - High enough concentrations will relax skeletal muscle (disorganization of the membrane??)

General Actions of Inhaled Anesthetics

- Cardiovascular System
  - Generalized reduction in arterial pressure and peripheral vascular resistance. Isoflurane maintains CO and coronary function better than other agents
- Central Nervous System
  - Increased cerebral blood flow and decreased cerebral metabolism

Toxicity and Side Effects

- Depression of respiratory drive
  - Decreased CO2 drive (medullary chemoreceptors), Takes MORE CO2 to stimulate respiration
- Depressed cardiovascular drive
- Gaseous space enlargement by NO
- Fluoride-ion toxicity from methoxyflurane
  - Metabolized in liver = release of Fluoride ions
    - Decreased renal function allows fluoride to accumulate = nephrotoxicity
- Malignant hyperthermia
  - Rapidly cool the individual and administer Dantrolene to block S.R. release of Calcium

Advantages and Disadvantages of Select Inhaled Anesthetics

- **Halothane**
  - Unpredictable occurrence of hepatitis & hepatic necrosis
  - nonflammable and nonirritating
  - MAY CAUSE MALIGNANT HYPERTHERMIA
- **Enflurane**
  - minimal side effects compared to other agents
  - Smooth adjustments to anesthesia with little change in pulse or respiratory rates
  - Not used in pediatric anesthesia
  - MAY CAUSE MALIGNANT HYPERTHERMIA

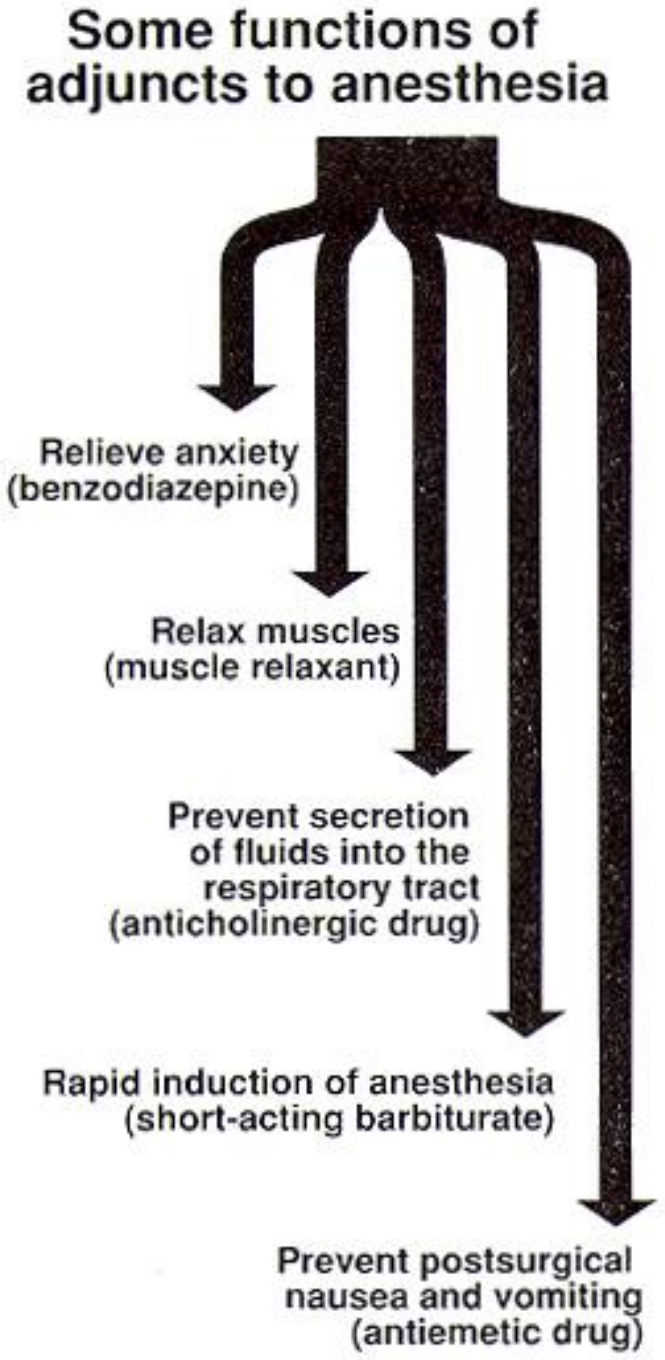
Advantages and Disadvantages of Select Inhaled Anesthetics

- Isoflurane
  - Cardiac output is maintained, and systemic vessels dilate
  - Arrhythmias are uncommon
  - Potentiates the actions of muscle relaxants
  - Cerebral blood flow and intracranial pressure are well controlled (preferred for neurosurgery)
  - Minimally metabolized and no reports of heptato- or nephrotoxicity
  - most widely used agent
  - MAY CAUSE MALIGNANT HYPERTHERMIA

Advantages and Disadvantages of Select Inhaled Anesthetics

- Desflurane
  - More irritating to airways than other agents
  - Rapid recovery, originally used in ambulatory surgery
  - No reports of malignant hyperthermia

Preanaesthetic Medication



Focus Points

1. Induction of anesthesia is through use of any of the IV agents (Barbiturates: Thiopental, Opiate: Fentanyl, Benzodiazepines: Midazolam, Dissociative: Ketamine, Others: Propofol, Etomidate and Droperidol)
2. Majntenance of anesthesia is through use of any of the ihalation agents

   -N2O (70% in oxygen) is not suitable alone

   - N2O is usually combined with another inhalation agent or with opioids e.g. fentanyl

A comparison

	halothane	N2O
Speed of induction	intermediate	fast
Potency	v.potent	weak
	MAC=2%	MAC 80%
Muscle relaxation	some	none
Cardiac arrhythmia	yes	no
Liver damage	yes	no
Recovery	slow	rapid

- NOTES:
- Enflurane releases flouride ions which may cause renal failure
- All inhalation anesthetics can cause resp.depression, myocardial depression, cardiac arrhythmias, hypotension and PONV
- A mixture of N2O(50-70%) and haothane 1% is usually used in anesthesia.

Nitrous Oxide

- Characterized by inert nature with minimal metabolism
- Colorless, odorless, tasteless, and does not burn

- Simple linear compound
- Only anesthetic agent that is inorganic
- Major difference is low potency
- MAC value is 105%
- Weak anesthetic, powerful analgesic
- Needs other agents for surgical anesthesia
- Low blood solubility (quick recovery)

Systemic effects

- Nitrous Oxide Systemic Effects
- Minimal effects on heart rate and blood pressure
- May cause myocardial depression in sick patients
- Little effect on respiration
- Safe, efficacious agent

Side effects

- Nitrous Oxide Side Effects
- Inhibits methionine synthetase (precursor to DNA synthesis)
- Inhibits vitamin B-12 metabolism
- Dentists, OR personnel, abusers at risk