

General Anesthetics

General Anesthetics:

There Are Two Types:

- ◎ Inhalational
- ◎ Intravenous

Inhaled Anesthetics:

- ◉ Nitrous Oxide (Gas)
- ◉ Halogenated Liquid Hydrocarbons:
 - Desflurane
 - Enflurane
 - Isoflurane
 - Halothane
 - Methoxyflurane
 - Sevoflurane

Inhaled Drugs: Pharmacokinetics

⊙ Absorption:

- Transfer of drug from alveolar air to blood

⊙ Distribution:

- Transfer of drug from blood to brain and other organs

Factors that Influence Absorption & Distribution:

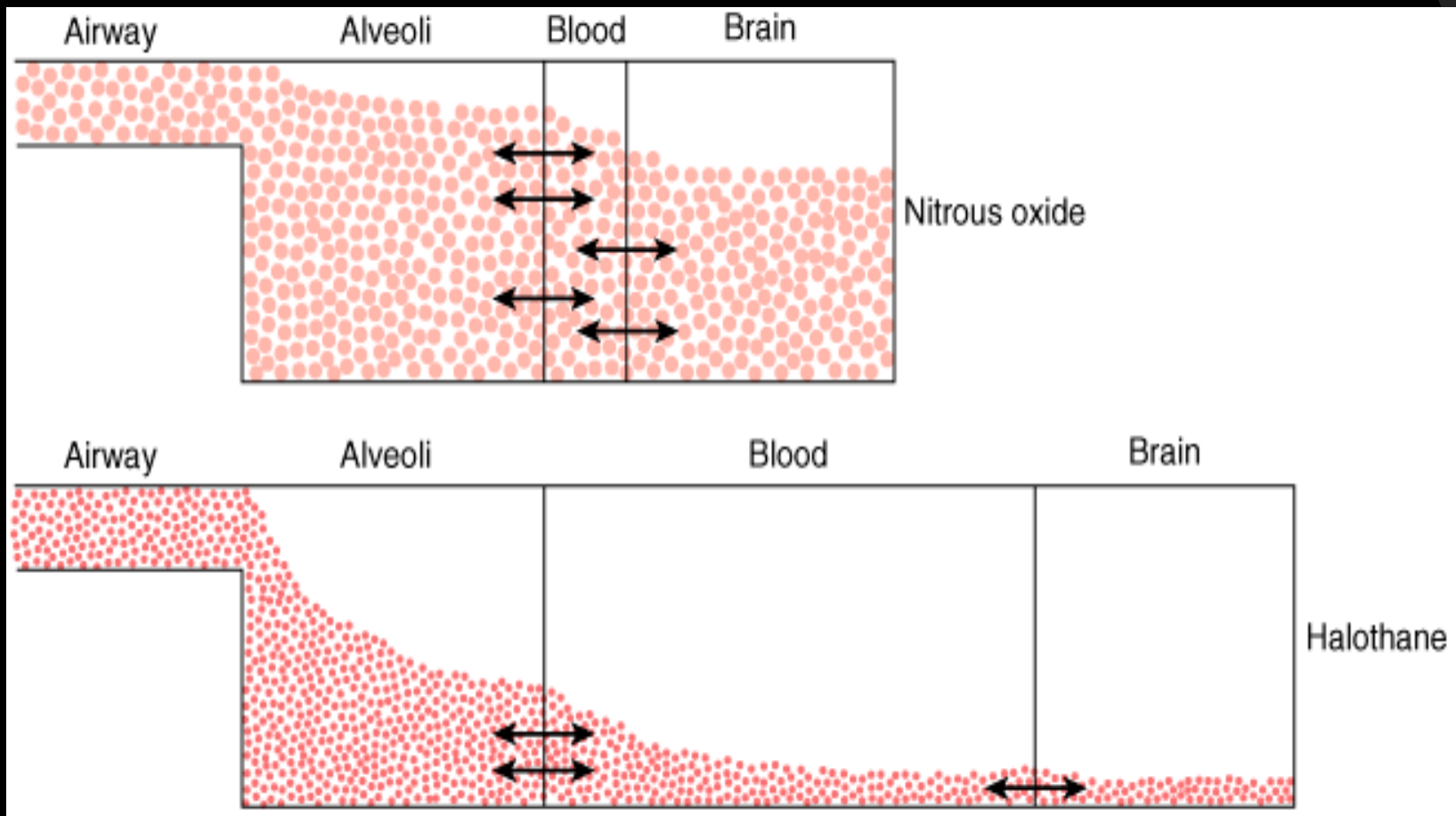
◎ 1. Solubility of Drug in Blood:

- Low Solubility in Blood: → Rapidly Saturate blood (Rapid rise of arterial partial pressure or tension of gas):→
 - Fast Onset of Action

◎ Blood / Gas Partition Coefficient:

- Is Index of Solubility and
- Defines relative affinity of an anesthetic for blood compared with that of inspired gas.

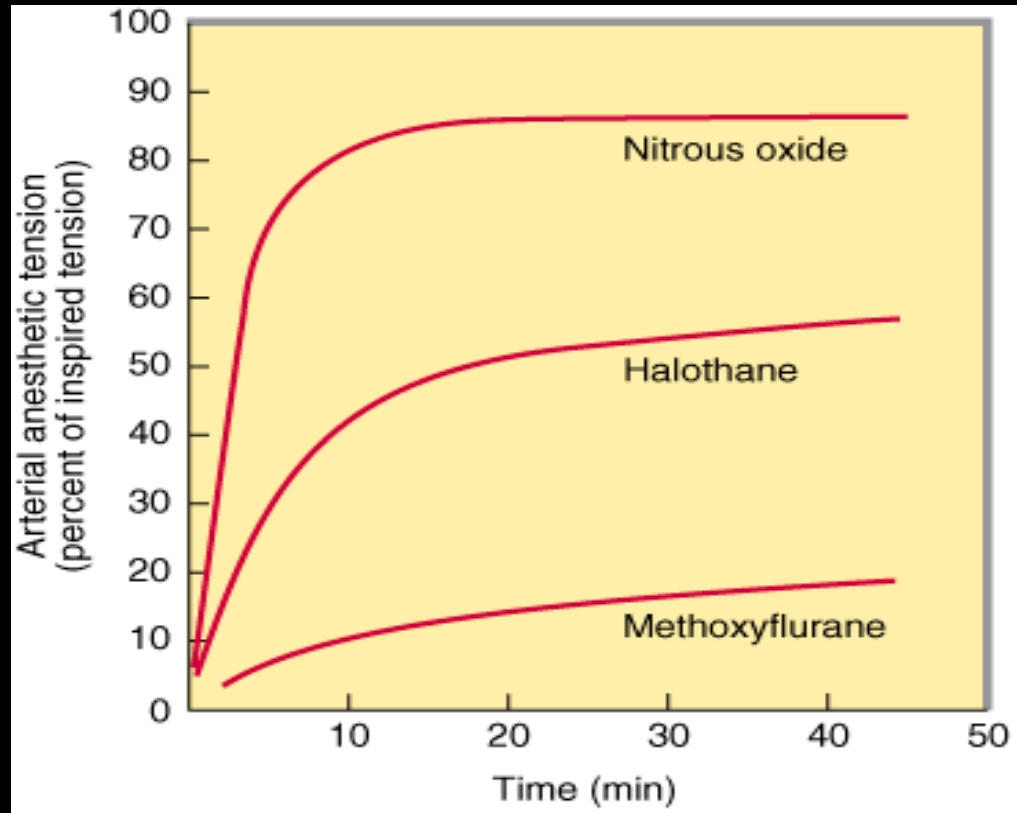
The more soluble: The more Time to Saturate Blood (\uparrow Partial Pressure of Drug)



Blood / Gas Partition Coefficient:

- ◎ **Low:** **Rapid** Onset of Anesthesia & Recovery
 - Desflurane, Sevoflurane, Nitrous Oxide
- ◎ **Moderate:** Intermediate Onset of Anesthesia
Enflurane, Halothane, Isoflurane
- ◎ **High:** **Slow** Onset of Anesthesia
 - Methoxyflurane, Ether
- ◎ So, There is **Inverse Relationship**

High Blood G.P.C: ↓Rate of rising Arterial Partial Pressure or tension of gas



Factors that Influence Absorption & Distribution:

◎ 2. Drug Concentration in Inspired Air:

- ↑ **Drug Concent:** ↑ Rate of transfer into blood according to Fick's law :
 - ↑ **Rate of Anesthesia Induction**

3. Pulmonary Ventilation:

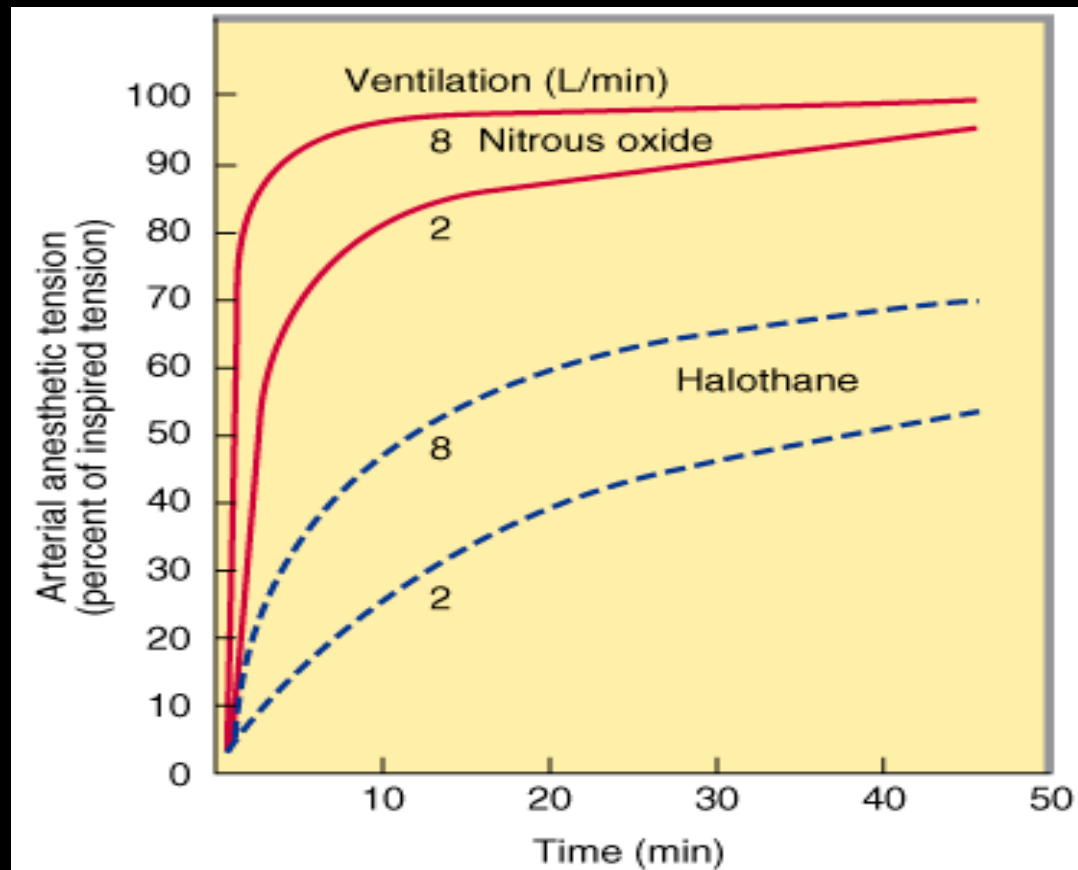
- ◎ Hyperventilation: ↑ Rate of Anesthesia Induction:

- Prominent for drugs that normally have a slow onset (Moderate-to-High Blood / Gas P.C.)
- Slight Increase for those with Low B.G.P.C

- ◎ Opioid Analgesics: → Hypoventilation:

- ↓Rate of Anesthesia Induction

Hyperventilation: Significantly \uparrow Arterial Tension of drugs with Moderate-to-High B.G.P.C



4. Pulmonary Blood Flow:

- ◎ ↑Pulmonary Blood Flow (↑Cardiac Output): →
 - ↑Time for Blood Saturation (due to ↑B. Volume): →
 - ↓Rate of Rise in Anesthetic tension &
 - ↓Rate of Anesthesia Induction
 - Significant for drugs with Moderate-to-High Blood / Gas P.C.

4. Pulmonary Blood Flow:

- ◎ Circulatory Shock:

- ↓ Cardiac Output + and Hyperventilation:
 - ↑ Induction of anesthesia with Halothane and Isoflurane

5. Arterio-Venous Concentration Gradient:

- ◎ ↑Gradient: ↑Uptake of drug by Highly Perfused Tissues:
 - ↓Pressure of drug in mixed venous blood
 - ↑Time to achieve equilibrium with brain tissue
 - ↓ Rate of Anesthesia Induction

Inhaled Anesthetics:

◎ Elimination:

- ↑Rate of Elimination: ↑Rate of Recovery

◎ Factors controlling Rate of Recovery:

- 1. ↓Blood G.P.C: ↑ Rate of recovery
- 2. ↓Solubility in brain tissue: ↑ Rate of recovery
- 3. ↑Duration of exposure to drug: ↓ Rate of recovery

Elimination:

- ◎ Lungs is the major route of elimination
- ◎ Hepatic Metabolism may also contribute to elimination of some volatile anesthetics:
 - Elimination of Halothane during recovery is more rapid than that of Enflurane

Hepatic Metabolism:

- ◎ Methoxyflurane > Halothane > Enflurane > Sevoflurane > Isoflurane > Desflurane > NO
- ◎ Methoxyflurane:
 - 70% metabolize: → Fluoride Ions → Nephrotoxicity
- ◎ Halothane: Under low O₂:
 - Free Radicals: → Hepatitis: rare

Hepatic Metabolism:

⊙ Enflurane & Sevoflurane:

- Low level fluoride ions: not toxic

⊙ Sevoflurane:

- Degraded by contact with CO₂ absorbent in anesthesia machines, yielding a vinyl ether called “Compound A”: which:
- Cause Renal Damage if high concentrations are absorbed

Mechanism of Action:

- ⦿ Facilitate Action of GABA
- ⦿ High Conc: Directly Activate GABA_A Receptors
- ⦿ Hyperpolarization via K⁺ Channel Activation
- ⦿ ↓Duration of Nicotinic Receptor Opening
- ⦿ ↑Glycine Channel Opening

General Anesthetics:

- ◎ Specific **Neurons** or neuronal pathways have **Different Sensitivity**:
 - 1. At low conc: **Neurons in Dorsal Horn** of spinal cord are inhibited: Analgesia
 - **Stage I of Anesthesia**
 - 2. **Blockade of Inhibitory Neurons**: → Excitation: **Stage II**: Excitement
 - Delirium, Irregular Respiration, Vomiting, Amnesia

Stages of Analgesia:

◎ Stage III:

- Blockade of ascending pathways in reticular activating system

◎ Stage IV: Cardio-respiratory Collapse

- Depression of vasomotor center in medulla
- Depression of respiratory system in brain stem so:
 - Neurons in respiratory and vasomotor centers are least sensitive

Inhaled Anesthetic Potency:

MAC (Minimum Alveolar Concentration):

- Concentration causing immobility in 50% of patients when exposed to a noxious stimulus (eg, surgical incision).
- It represents **ED₅₀**.

Inhaled Anesthetic Potency:

Anesthetic	MAC
Nitrous Oxide	>100
Desflurane	6-7
Sevoflurane	2.0
Isoflurane	1.4
Enflurane	1.7
Halothane	0.75
Methoxyflurane	0.16

Inhaled Anesthetic Potency:

- ◎ **Nitrous Oxide** >100 : Low Potency
 - Can not produce surgical anesthesia by itself and
 - Used with volatile or IV anesthetics to produce a state of balanced anesthesia

Inhaled Anesthetic Potency:

- ◎ 1MAC, 2MAC,.....
 - A dose of **1 MAC** of any anesthetic prevents movement in response to surgical incision in **50%** of patients
 - **1.1 MAC: 95%....**
- ◎ MAC gives no information about slope of dose-response curve.
- ◎ Dose-response relationship for inhaled anesthetics is very steep.

MAC:

⊙ ↓MAC:

- Elderly patients
- Hypothermia
- Opioid Analgesics
- Sympatholytics
- Sedative-hypnotics

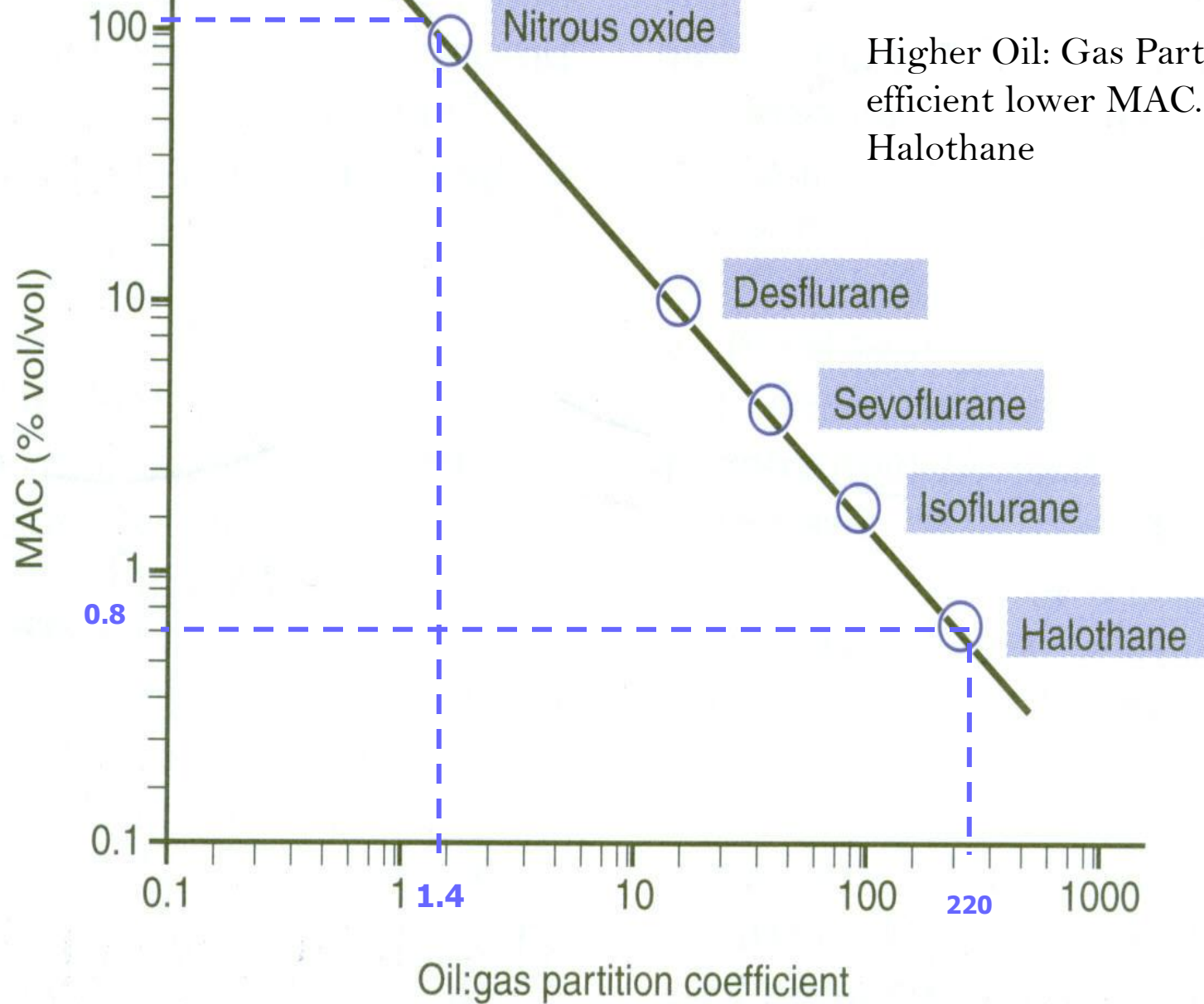
MAC:

- ⊙ MAC: not affected greatly by sex, height, and weight.
- ⊙ **↑MAC:** Chronic use of centrally active drugs, alcohol abuse, and pregnancy
- ⊙ **MACs are additive.**
 - Nitrous oxide (60–70% as a carrier gas) 40% of a MAC: ↓ thereby anesthetic requirement

MAC:

- ◎ ↑Lipid Solubility: ↑ Potency: ↓MAC
- ◎ Lipid Solubility:
 - Oil: Gas Partition Co-efficient
 - Brain-Blood Partition Co-efficient
 - ↑ Brain-Blood P.C: ↓Rate of Recovery

OIL GAS PARTITION CO-EFFICIENT



Inhalation Anesthetic	MAC value %	Oil: Gas Partition C.
Nitrous oxide	>100	1.4
Desflurane	7.2	23
Sevoflurane	2.5	53
Isoflurane	1.3	91
Halothane	0.8	220

Halogenated Anesthetics:

Anesthetic	Blood-Gas P.C	Brain-Blood P.C	MA C	Onset & Recovery
Enflurane	1.8	1.4	1.7	Medium
Isoflurane	1.4	2.6	1.4	Medium
Sevoflurane	0.69	1.7	2.0	Rapid

Organ System Effects of Inhaled Anesthetics

Cardiovascular System:

- ◎ **↓BP:** Most of them
 - Hypercapnia releases catecholamines: ↑BP
- ◎ **Bradycardia:** Halothane: Direct Vagal Stimulation
- ◎ **Tachycardia:** Desflurane and Isoflurane
- ◎ Desflurane:
 - Transient sympathetic activation with elevations in catecholamine levels
 - ↑Heart rate and BP

Cardiovascular System:

◎ ↓Myocardial Function:

- Enflurane and Halothane: Greater effects than Isoflurane and Others

◎ Ventricular Arrhythmias:

- More likely: Halothane and Isoflurane
- Less Likely: Sevoflurane and Desflurane

Ventricular Arrhythmias:

◎ More likely: In Patients:

- Using Sympathomimetic Drugs or
- ↑Endogenous Catecholamines:
 - Anxious Patients
 - Epinephrine-containing local anesthetics,
 - Inadequate Intraoperative anesthesia or analgesia
 - Pheochromocytomas

Respiratory System:

- ◎ All are respiratory depressants:
 - Isoflurane and **Enflurane: Most Depressant**
- ◎ All increase resting level of PaCO_2
- ◎ ↓ Mucociliary function in airway
- ◎ All are **Bronchodilator**:
 - **Halothane & Sevoflurane**: Potent in this respect &
 - Choice in (Asthma, Bronchitis, COPD).
- ◎ Some are Pungent: Desflurane

Effects on Brain:

- ◎ ↑Cerebral Blood Flow: → ↑ICP:
 - Least Likely: Nitrous Oxide
 - Less with Desflurane and Sevoflurane
 - Hyperventilation: ↓Risk of ↑ICP
- ◎ Seizure-Like EEG Activity:
 - Not seen with Desflurane
- ◎ Analgesic and Amnesic Effect:
 - Specific to Nitrous Oxide

Effects on Kidney:

- ◎ ↓GFR
- ◎ ↓Renal Blood Flow
- ◎ Autoregulation of renal flow may be impaired by these drugs.

Effects on Liver

- ◎ ↓Hepatic Blood Flow: Dose -Dependent
- ◎ No Permanent changes in liver enzyme function except following repeated exposures to halothane.

Effects on Uterine Smooth Muscle:

◎ Relaxation:

- Nitrous Oxide: Little Effect
- Halogenated Anesthetics: Potent effect in a Dose-dependent fashion

Side Effects of Inhaled Anesthetics

Side Effects:

◎ Hepatotoxicity (Halothane):

- More likely in Obese with previous exposure during short time interval
- Caused by free radicals or immune-mediated responses
- Trifluoroacetylated (TFA) proteins in liver could be formed

Side Effects:

- ◎ **Nephrotoxicity:** Methoxyflurane
- ◎ **Malignant Hyperthermia:** Rare
 - Autosomal dominant genetic disorder of skeletal muscle
 - Occurs with Inhaled Drugs and muscle relaxants (eg, succinylcholine)
 - Tachycardia, HTN, Severe Muscle Rigidity, Hyperthermia, Hyperkalemia, and Acid-Base Imbalance with Acidosis

Malignant Hyperthermia:

- ◎ **Cause:** ↑calcium in skeletal muscle cells
- ◎ **Rx:**
 - **Dantrolene:** ↓Ca²⁺ release from sarcoplasmic reticulum
 - ↓**Temperature** and Restore electrolyte and acid-base balance

Chronic Side Effects:

- ◎ ↑ **Cancer** Rate in operating room personnel (Some studies reported)
- ◎ ↑ Incidence of **Miscarriages** in female personnel (Some studies reported)
- ◎ ↑ Risk of **Abortion** in Pregnant Patients
- ◎ Nitric Oxide:
 - ↓ Methionine Synthase Activity
 - ↑ Risk of Megaloblastic Anemia

Intravenous Anesthetics

IV Anesthetics:

- ◉ Etomidate
- ◉ Ketamine
- ◉ Methohexital
- ◉ Midazolam
- ◉ Propofol
- ◉ Thiopental

IV Anesthetics:

- Most of them: **Rapid Onset of Action:**
 - Faster than the most rapid inhaled agents (Desflurane and Sevoflurane)
 - Commonly used for induction of anesthesia
 - Fentanyl & Midazolam: Slow Onset & Recovery

IV Anesthetics:

- ◎ Most of them: **Recovery is Rapid**
 - Propofol: Recovery time is similar to Sevoflurane and Desflurane
 - Midazolam: Slow Recovery
- ◎ Most of them: **Lack Analgesic Effect**
 - Adjunctive use of potent opioids (Fentanyl,...) is needed.

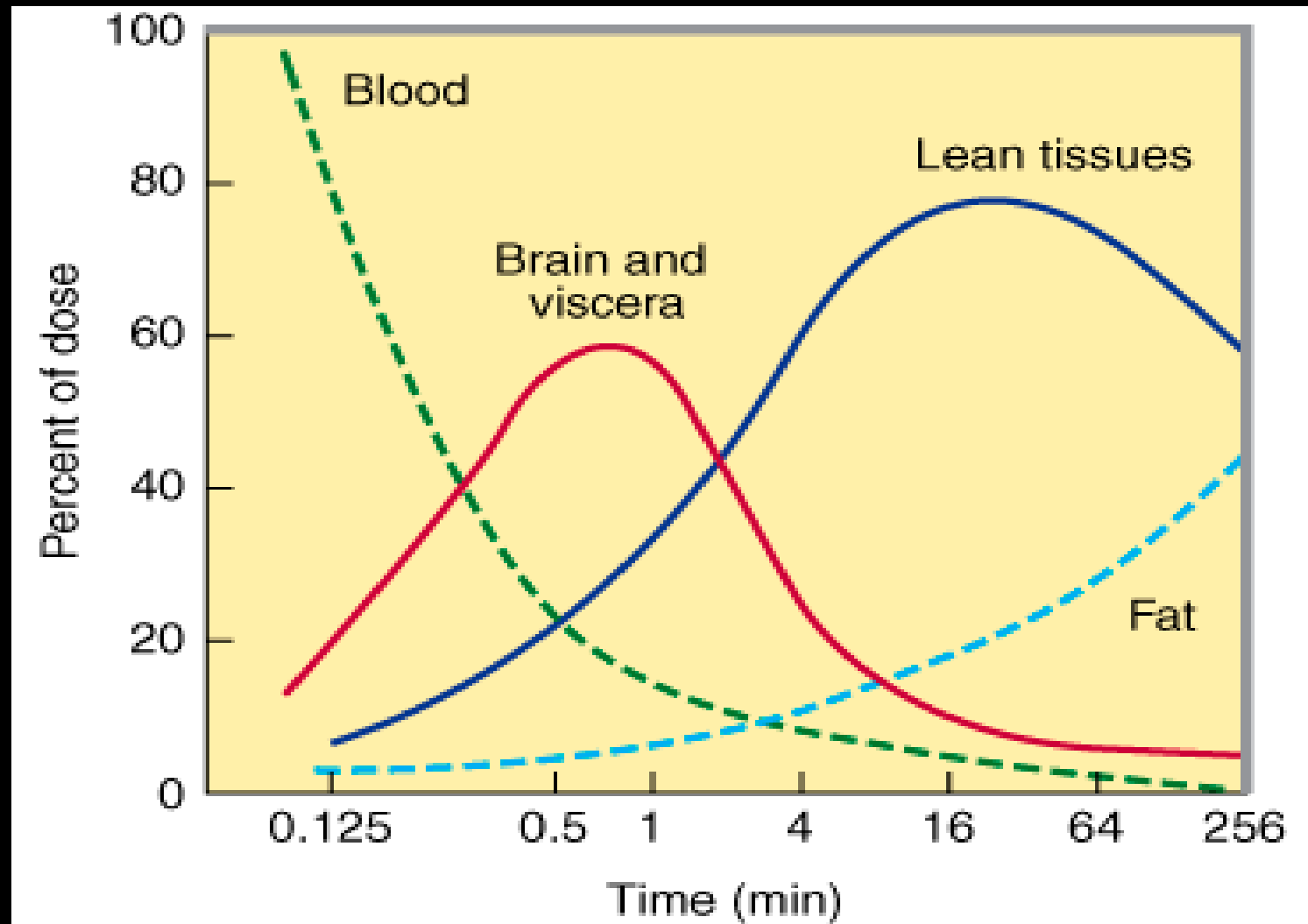
Barbiturates:

- ◎ **Thiopental:** Commonly used for induction of anesthesia.
- ◎ **Thiamylal:** Structurally almost identical to thiopental
- ◎ **Methohexital**

Thiopental (Nesdonal):

- ◎ Has high lipid solubility and rapidly crosses BBB
- ◎ Produces unconsciousness in < 1 minute, then:
- ◎ Rapidly diffuses out of Brain and other highly vascular tissues and is Redistributed to Muscle and Fat

Redistribution of Thiopental:



Thiopental (Nesdonal):

- ◎ It is Metabolized slowly & less than 1% is excreted unchanged by kidney.
- ◎ ↓BP & Cardiac Output
- ◎ Respiratory depressant effect
- ◎ It can be used for rapid control of seizures.

Thiopental (Nesdonal):

◎ Brain Effects:

- ↓ Cerebral metabolism and oxygen utilization
- ↓ Cerebral Blood Flow
- **It does not increase ICT:**
 - Desirable drug for patients with cerebral swelling (Head Trauma, Brain Tumors)

Methohexital:

◎ Central Excitatory Activity:

- Useful for Surgery involving ablation of seizure foci

◎ Antiseizure Activity:

- Drug of choice for Anesthesia in patients undergoing ECT
- Preferred over thiopental for short ambulatory procedures (Due to More rapid elimination)

Barbiturates:

- ⦿ ↓Hepatic Blood Flow and GFR
- ⦿ Exacerbate Acute Intermittent Porphyria by
↑Aminolevulinic acid (ALA) synthase
- ⦿ Thiopental: Porphyric Crisis: Rare

Benzodiazepines:

- ◎ **Preanesthetic Medications:** Due to their sedative, anxiolytic, and amnestic effects:
 - Diazepam
 - Lorazepam
 - Midazolam

Midazolam:

- ◎ BZDs of choice for Parenteral Administration
- ◎ Water-Soluble
- ◎ Diazepam and Lorazepam:
 - Not water-soluble
 - Their IV use necessitates nonaqueous vehicles, which cause pain and local irritation.
- ◎ High Incidence of Amnesia (> 50%)

Midazolam:

- ⦿ Has a more rapid onset
- ⦿ Shorter elimination half-life (2–4 hours)
- ⦿ Steeper dose-response curve than other BZDs
- ⦿ Flumazenil:
 - Accelerate recovery in case of excessive doses (especially in elderly patients)

Opioid Analgesics:

- ◉ Morphine
- ◉ Fentanyl
- ◉ Alfentanil
- ◉ Sufentanil
- ◉ Remifentanil:
 - Potent and Extremely Short-Acting Opioid
 - Minimum Residual Ventilatory Depression

Opioid Analgesics:

◎ High Doses of Opioids During Surgery:

- Chest wall (and laryngeal) rigidity, thereby acutely impairing ventilation
- ↑Postoperative opioid requirements owing to development of acute tolerance

◎ Lower doses of Fentanyl and Sufentanil:

- As an adjunct to both IV and inhaled anesthetics to provide perioperative analgesia

Opioid Analgesics:

◎ Droperidol:

- A Butyrophenone Related to Haloperidol
- Is Antiemetic and Tranquilizer

◎ Droperidol + Fentanyl:

- Produce analgesia and amnesia and combined with nitrous oxide provide a state referred to as **Neuroleptanesthesia**

Propofol:

- ◎ Commonly used IV anesthetic
- ◎ Rapid Onset of Action (Similar to IV Barbiturates)
- ◎ More Rapid recovery than Barbiturates
- ◎ Anti-emetic: ↓ Postoperative N & V

Propofol:

- Used for both induction and maintenance of anesthesia as part of total IV or balanced anesthesia techniques
- Agent of choice for ambulatory surgery
- Effective in producing prolonged sedation (Anxiolytic) in patients in critical care settings
- Prolonged Use:→ ↑Serum lipid level, Acidosis

Propofol:

- ⦿ Rapidly metabolized in liver at a rate ten times faster than that of thiopental.
- ⦿ Excreted in urine as glucuronide and sulfate conjugates
- ⦿ Total body clearance is greater than hepatic blood flow:
 - Has Extrahepatic mechanisms in addition to metabolism by liver enzymes.

Propofol:

- ⊙ Effects on respiratory function are similar to those of thiopental.
- ⊙ ↓BP through ↓ peripheral arterial resistance and venodilation
- ⊙ Greater direct negative inotropic effects than other IV anesthetics
- ⊙ Pain at the site of injection is the most common adverse effect of bolus administration.

Newer Formulations of Propofol:

◎ Ampofol:

- Contain less lipid to ↓ risk of contamination but:
- ↑ Pain at injection site: Admixture or pretreatment with lidocaine (20–50 mg) is needed

◎ Fospropofol:

- Water-Soluble Prodrug of Propofol

Etomidate:

- ⦿ Used for Induction of Anesthesia
- ⦿ Major Advantage: **Minimal Cardiovascular and Respiratory Depression**
- ⦿ No Analgesic Effect
- ⦿ Less Rapid Recovery (< 10 min) compared with Propofol

Etomidate:

- ⊙ Short Acting: Due to:
 - Redistribution of the drug from brain to highly perfused tissues
- ⊙ Pain on injection, Pro-Convulsant Activity
- ⊙ ↑ Postoperative N & V

Etomidate:

- ⊙ Adrenocortical Suppression via inhibitory effects on steroidogenesis
- ⊙ ↓ Cortisol after a single dose
- ⊙ Prolonged infusion in critically ill patients:
 - Hypotension
 - Electrolyte Imbalance
 - Oliguria

Ketamine:

- ⦿ It Blocks NMDA Receptor of Glutamic Acid
- ⦿ The only IV anesthetic that possesses:
 - Both anesthetic and Analgesic Effect
 - Ability to produce dose-related Cardiovascular Stimulation:
 - ↑Heart Rate, BP, and Cardiac Output
 - Dangerous for Hypertensive and IHD

Ketamine:

◎ Cardiovascular Stimulation:

- Stimulate central sympathetic nervous system and
- Inhibit Reuptake of NE
- Useful for High-Risk Patients in Cardiogenic or Septic shock

◎ Similar to Inhaled A: ↑ICP, Cerebral Blood flow and oxygen consumption

Ketamine:

- ◎ ↓Respiratory Rate: but airway reflexes are preserved
- ◎ Postoperative Disorientation, Sensory and Perceptual Illusions, and Vivid Dreams (Emergence Phenomena):
 - ↓ BY Diazepam, Midazolam, Propofol

Ketamine:

- ◎ Useful in children undergoing painful procedures (**Dressing Changes for Burns**)
- ◎ Topical: Useful for some types of **Arthritic Pain**
- ◎ Produces a **Dissociative Anesthetic State**:
 - Catatonia, Amnesia, and Analgesia, with or without loss of consciousness (hypnosis).

