General Anesthetics

What are General Anesthetics?

- A drug that brings about a reversible loss of consciousness.
  - Depresses the nervous system
- These drugs are generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery.
- Anesthetic state
  - Collection of component changes in behavior or perception
    - Amnesia, immobility in response to stimulation, attenuation of autonomic responses to painful stimuli, analgesia, and unconsciousness

Purposes of General Anesthesia: (Inhaled and Intravenous)

- Amnesia
- Analgesia
- Immobility (muscle relaxation)
- Loss of consciousness
- Hypnosis
- Suppression of noxious reflexes

Essential Components of Anesthesia

- Analgesia- perception of pain eliminated
- Hypnosis- unconsciousness
- Depression of spinal motor reflexes
- Muscle relation

* These terms together emphasize the role of immobility and of insensibility!

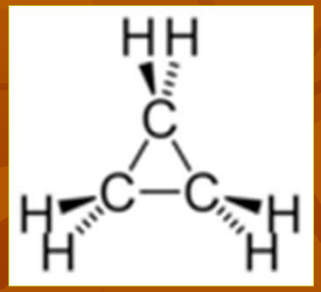
Background

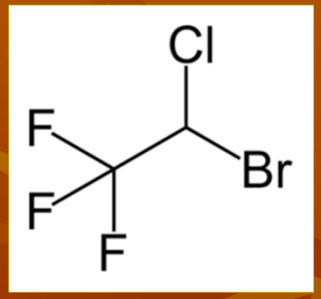
- **General anesthesia was absent until the mid-1800's**
- **William Morton** administered ether to a patient having a neck tumor removed at the Massachusetts General Hospital, Boston, in October 1846.
- The discovery of the **diethyl ether** as general anesthesia was the result of a search for means of eliminating a patient's pain perception and responses to painful stimuli.

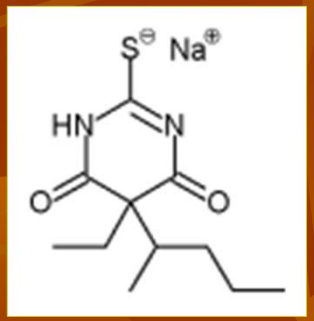
$(CH_3CH_2)_2O$

Diethyl-ether

- Cyclopropane: 1929
  - Most widely used general anesthetic for the next 30 years
- Halothane: 1956
  - Team effort between the British Research Council and chemists at Imperial Chemical Industries
  - Preferred anesthetic of choice
- Thiopental: Intravenous anesthetic







Hypotheses of General Anesthesia

1. Lipid Theory: based on the fact that anesthetic action is correlated with the oil/gas coefficients.
   - The higher the solubility of anesthetics is in oil, the greater is the anesthetic potency.
   - Meyer and Overton Correlations
   - Irrelevant
   - Cut-off phenomen

2. Protein (Receptor) Theory: based on the fact that anesthetic potency is correlated with the ability of anesthetics to inhibit enzymes activity of a pure, soluble protein. Also, attempts to explain the $GABA_A$ receptor is a potential target of anesthetics acton. Luciferase enzyme. (Firebug)

Other Theories

- Binding theory:
  - Anesthetics bind to hydrophobic portion of the ion channel

Meyer-Overton Correlation

- Has been used to describe the mechanism of volatile anesthetics
- Linear relationship between potency and lipid solubility
- No longer accepted universally
- Does appear in different levels of CNS integration
  - Molecular, subcellular and cellular mainly

Current Views of Anesthetic Mechanism

- Solubilization within the neuronal membrane
  - Redistribution of lateral pressures
  - Alters conformation of membrane proteins (i.e. Na^+ pump)
- Anesthetics interact with many hydrophobic sites
  - Protein structures that form ion channels
- Inhaled anesthetics act at lipid bilayer-protein interface
- Weak electrostatic forces between membrane protein and anesthetic
- Stimulation of K^+ leak channels (neuronal hyperpolarization)
- Ca^{+2} sensitivity to general anesthesia

Mechanism of Action

Not exactly known!

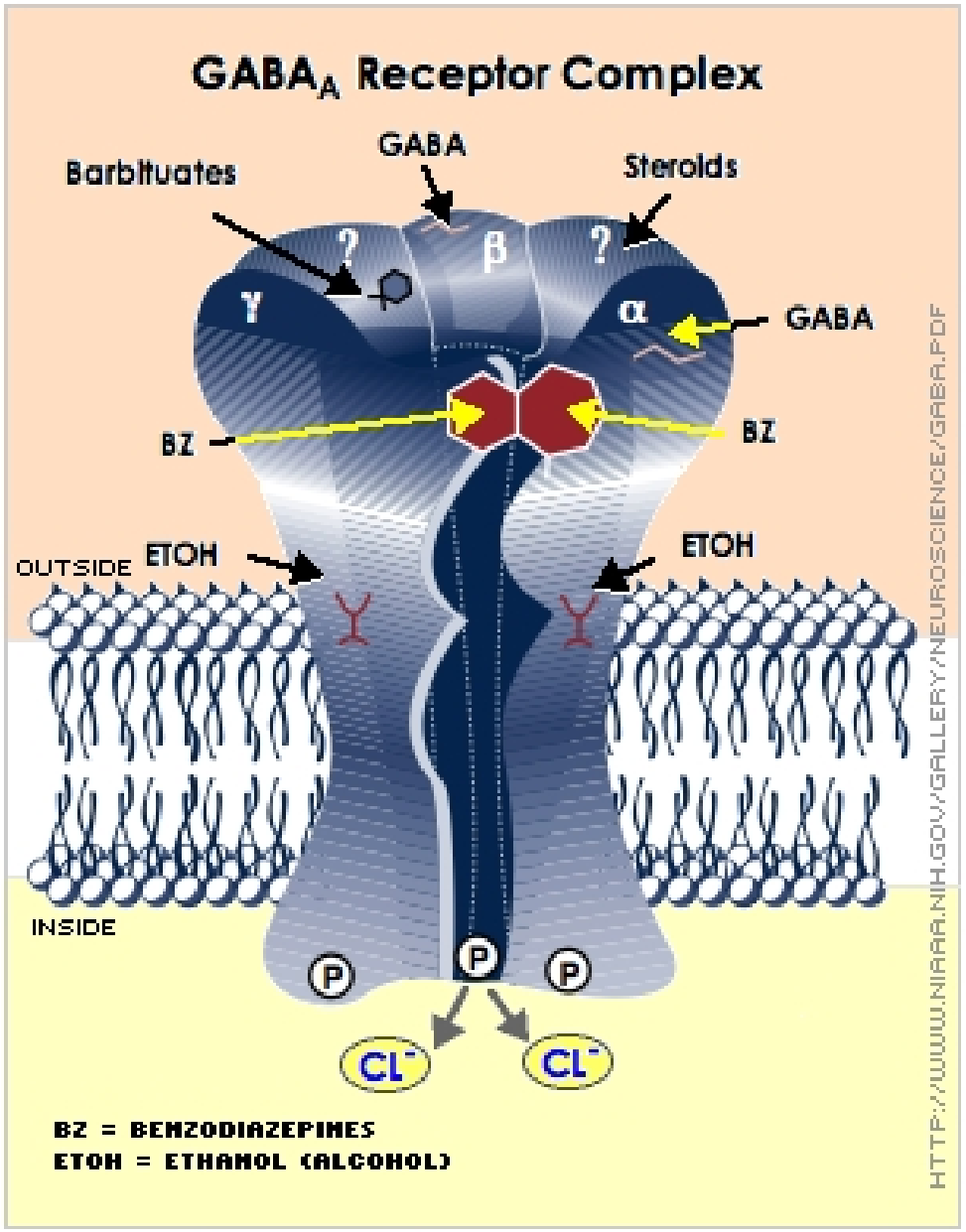
- Most Recent Studies:
  - General Anesthetics acts on the CNS by modifying the electrical activity of neurons at a molecular level by modifying functions of ION CHANNELS.
  - This may occur by anesthetic molecules binding directly to ion channels or by their disrupting the functions of molecules that maintain ion channels.

Mechanism (cont.)

- Scientists have cloned forms of receptors in the past decades, adding greatly to knowledge of the proteins involved in neuronal excitability. These include:
  - Voltage-gated ion channels, such as sodium, potassium, and calcium channels
  - Ligand-gated ion channel superfamily and
  - G protein-coupled receptors superfamily.

Receptors where general anesthetics act

- GABA-A receptor
- Glicin receptor
- neuronal nicotinic receptor
- ionotrop NMDA receptor


GABA$_A$ Receptor Complex
Barbituates
GABA
Steroids
?
β
?
γ
α
GABA
BZ
BZ
OUTSIDE
ETOH
ETOH
INSIDE
P
P
P
Cl$^-$
Cl$^-$
BZ = BENZODIAZEPINES
ETOH = ETHANOL (ALCOHOL)
HTTP://WWW.NIAAA.NIH.GOV/GALLERY/NEUROSCIENCE/GABA.PDF

- GABA
  - Key inhibitory NT within the brain
  - Two types (A and B)
  - GABA-A receptors increase Cl^- conductance (postsynaptic)
  - Analogous ligands (agonists) aside from GABA interact with GABA receptors
    - Benzodiazepines, barbiturates, anesthetic steriods, volatile anesthetics and ethanol

GABA-A/B/C

- GABA-A: individual expression of the GABA-A receptor subunit composition and subunit isoforms can modify response to anesthetic
- GABA-B: linked via G proteins to K^+ channels
  - Activated—GABA-B receptors decrease Ca^{+2} conductance and inhibit cAMP production
  - No KNOWN association with anesthesia
- GABA-C: also ligand-gated Cl^- channels

Levels of anesthesia

- I. Std. Analgesiae
- II. Std. Excitationis
- III. Std. Tolerantiae
  - III/1.
  - III/2.
  - III/3.
  - III/4.
- IV. Std. Asphyxiae

Guedel 1937
Diethylether

Ideal narcotic

- Rapid onset
- Wide th window
- Excretion in unchanged form
- No tissue damage
- Enough effective to let space to oxigen
- Fast diffusion – easy to set
- Not explosive and flammable

Premedication

- Fasting
- Sedatives
- BZD, Barb, antihistamine
- Analgesics
- Antiemetics
- Parasympatholytics

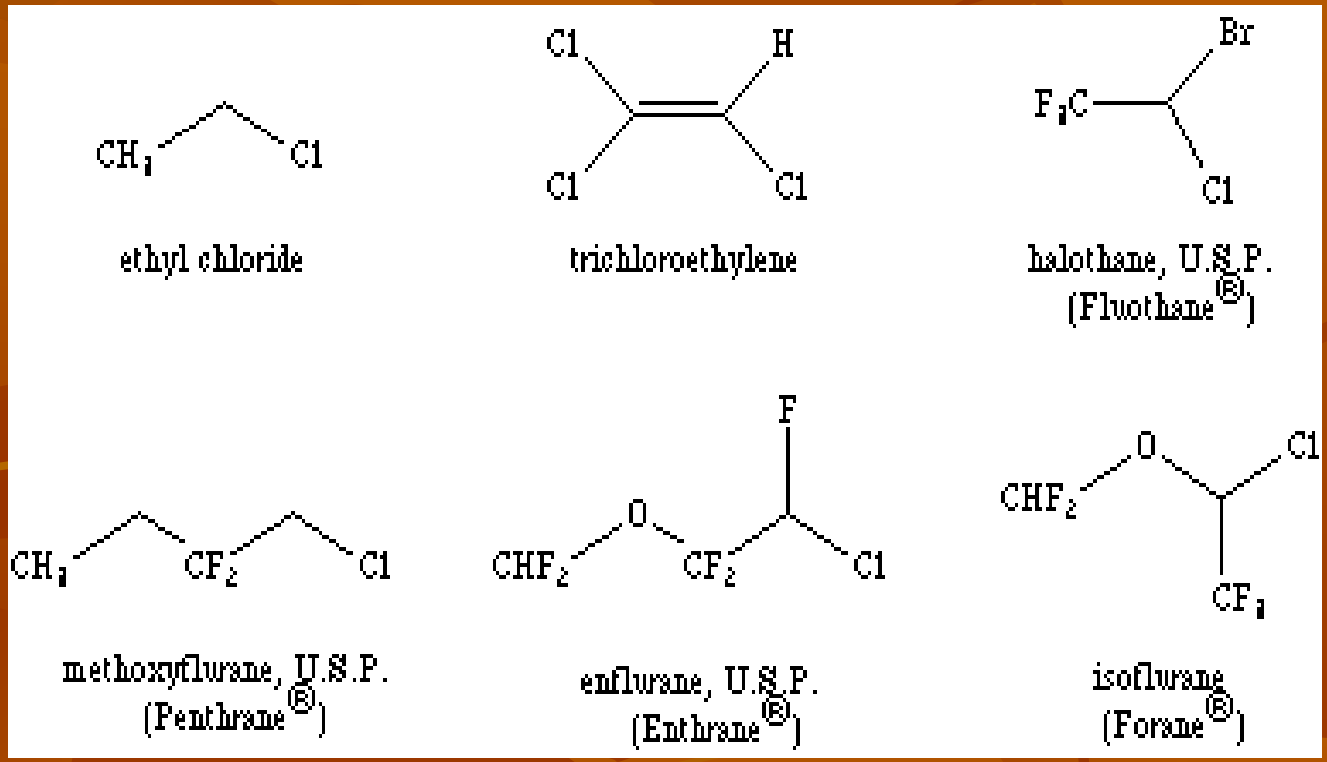
Anesthetics divide into 2 classes:

- **Inhalation** Anesthetics
  - Gasses or Vapors
  - Usually Halogenated
- **Intravenous** Anesthetics
  - Injections
  - Anesthetics or induction agents

Inhaled Anesthetics

Volatile fluids

- Halothane
- Enflurane
- Isoflurane
- Desflurane

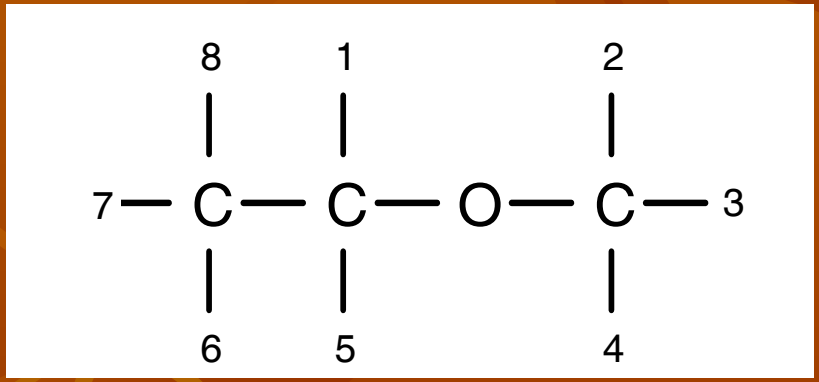


Halogenated compounds:
- Contain Fluorine and/or bromide
- Simple, small molecules

Physical and Chemical Properties of Inhaled Anesthetics

- Although halogenations of hydrocarbons and ethers increase anesthetic potency, it also increase the potential for inducing cardiac arrhythmias in the following order F<Cl<Br.1
- Ethers that have an asymmetric halogenated carbon tend to be good anesthetics (such as Enflurane).
- Halogenated methyl ethyl ethers (Enflurane and Isoflurane) are more stable, are more potent, and have better clinical profile than halogenated diethyl ethers.
- fluorination decrease flammibity and increase stability of adjacent halogenated carbons.
- Complete halogenations of alkane and ethers or full halogenations of end methyl groups decrease potency and enhances convulsant activity. Flurorthyl ($CF_3CH_2OCH_2CF_3$) is a potent convulsant, with a median effective dose (ED50) for convulsions in mice of 0.00122 atm.
- The presence of double bonds tends to increase chemical reactivity and toxicity.

Overview

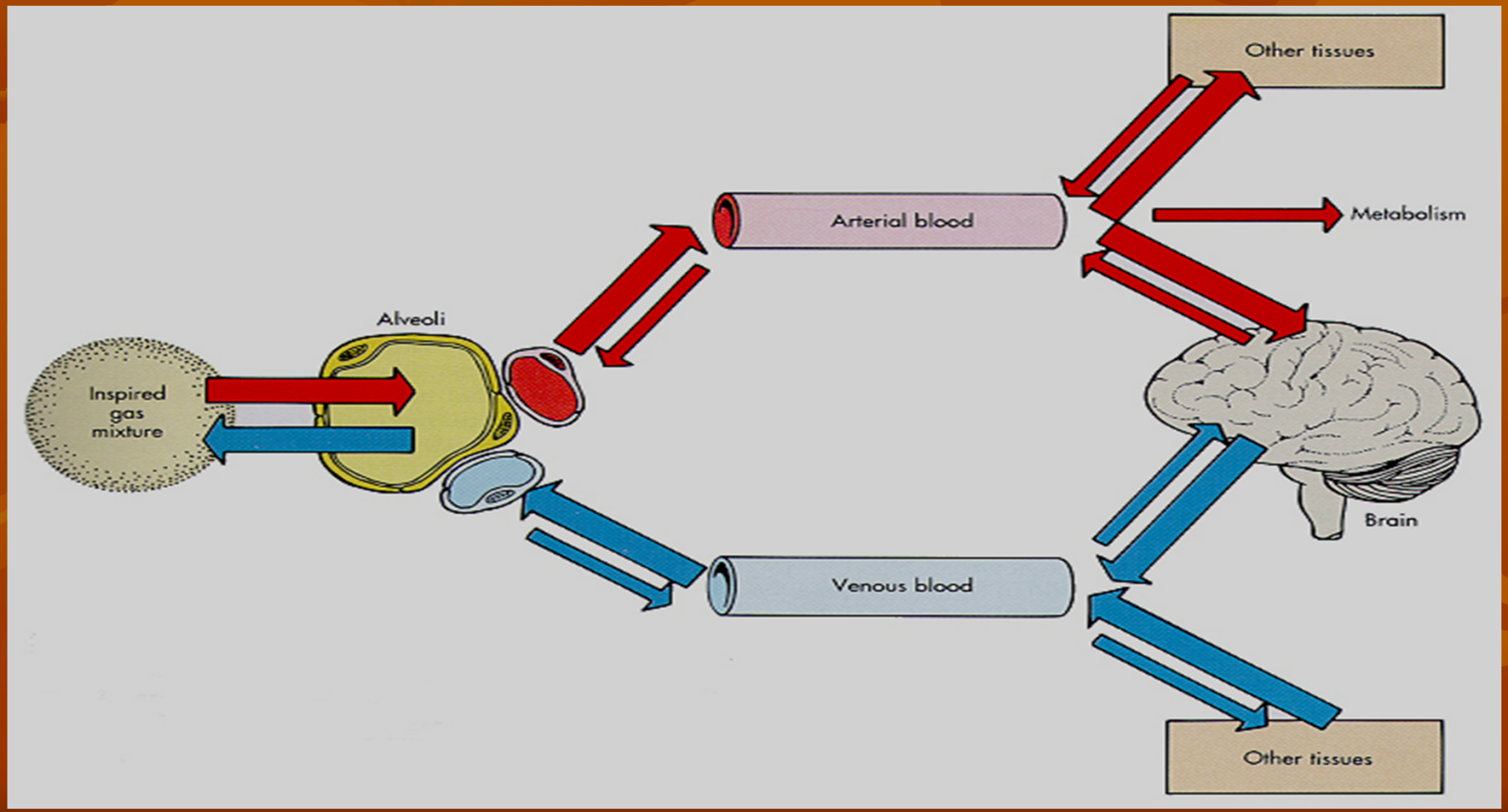


	MW	1	2	3	4	5	6	7	8
Diethyl ether	74	H	H	CH_3	H	H	H	H	H
Fluroxene	126	H	H	$=CH_2$		H	F	F	F
Methoxyflurane	165	F	H	H	H	F	Cl	H	Cl
Desflurane	168	H	F	H	F	F	F	F	F
Isoflurane	184	H	F	H	F	Cl	F	F	F
Enflurane	184	F	F	H	F	F	Cl	H	F
Sevoflurane	200	H	H	F	H	CF_3	F	F	F

Pharmacokinetics of Inhaled Anesthetics

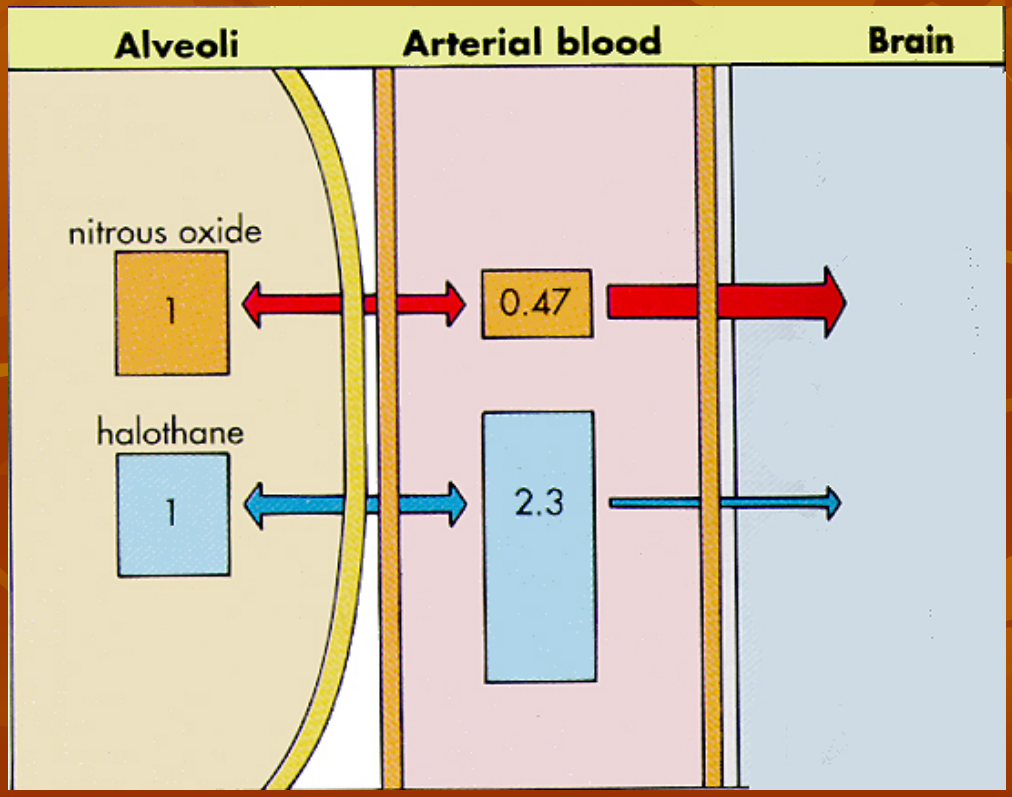
1. Amount that reaches the brain
    1. Indicated by oil:gas ratio (lipid solubility)
2. Partial Pressure of anesthetics
    1. 5% anesthetics = 38 mmHg
3. Solubility of gas into blood
    1. The lower the blood:gas ratio, the more anesthetics will arrive at the brain
4. Cardiac Output
    1. Increased CO= greater Induction time

Pathway for General Anesthetics



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

LOW solubility in blood= fast induction and recovery
HIGH solubility in blood= slower induction and recovery.



MAC

MINIMUM ALVEOLAR CONCENTRATION

- A measure of potency
- 1 MAC is the concentration necessary to prevent responding in 50% of population.
- Values of MAC are additive:
  - Avoid cardiovascular depressive concentration of potent agents.

Table 19–1

Properties of Inhalational Anesthetic Agents

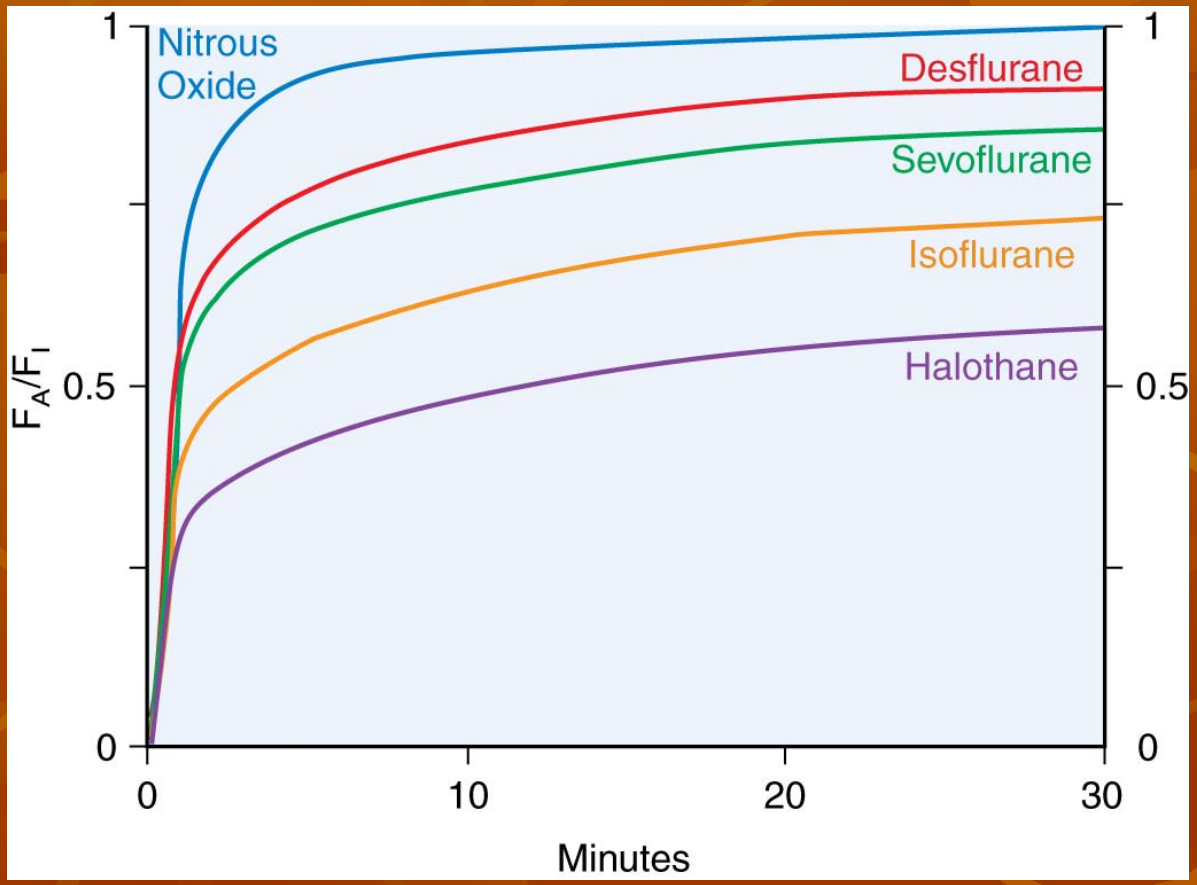
ANESTHETIC AGENT	MAC[a] (vol %)	MAC_{AWAKE}[b] (vol %)	EC_{50}[c] FOR SUPPRESSION OF MEMORY (vol %)	VAPOR PRESSURE (mm Hg at 20°C)	PARTITION COEFFICIENT AT 37°C			RECOVERED AS METABOLITES (%)
					Blood:Gas	Brain:Blood	Fat:Blood	
Halothane	0.75	0.41	—	243	2.3	2.9	51	20
Isoflurane	1.2	0.4	0.24	250	1.4	2.6	45	0.2
Enflurane	1.6	0.4	—	175	1.8	1.4	36	2.4
Sevoflurane	2	0.6	—	160	0.65	1.7	48	3
Desflurane	6	2.4	—	664	0.45	1.3	27	0.02
Nitrous oxide	105	60.0	52.5	Gas	0.47	1.1	2.3	0.004
Xenon	71	32.6	—	Gas	0.12	—	—	0

[a]MAC (minimum alveolar concentration) values are expressed as vol %, the percentage of the atmosphere that is anesthetic. A value of MAC greater than 100% means that hyperbaric conditions would be required.

[b]MAC_{awake} is the concentration at which appropriate responses to commands are lost.

[c]EC_{50} is the concentration that produces memory suppression in 50% of patients. —, Not available.

Increase in Anesthetic Partial Pressure in Blood is Related to its Solubility



Uptake of inhalational general anesthetics. The rise in end-tidal alveolar (FA) anesthetic concentration toward the inspired (FI) concentration is most rapid with the least soluble anesthetics, nitrous oxide and desflurane, and slowest with the most soluble anesthetic, halothane. All data are from human studies.

Significance of solubility
Agents of low solubility in blood included
- -Nitrous oxide
- -Desflurane
- -Sevoflurane

•With low solubility the partial pressure in blood rises quickly

Agents of medium solubility in blood included:
- • Halothane
- • Isofulane

•With medium solubility in blood partial pressure in blood raises slowly

General Actions of Inhaled Anesthetics

- Respiration
  - Depressed respiration and response to CO2
- Kidney
  - Depression of renal blood flow and urine output
- Muscle
  - High enough concentrations will relax skeletal muscle

Cont'

- 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

Toxicity and Side Effects

- Malignant hyperthermia
  - Rapidly cool the individual and administer Dantrolene to block S.R. release of Calcium

Diethylether

- Boiling point 35 C
- 1 ml = 60 drops
- Non-stable (degraded: dioxiethylperoxide and acetaldehyde)
- High muscle relaxant effect (increase the effectiveness of curare)
- 30000:1 death
- Airway irritation, secretion increases
- Nausea, vomitus
- Elimination - lungs

Halothane

- Light sensitive (amber bottle with preservative thymol)
- Not explosive, not flammable
- 4-5 x higher effectiveness than ether, MAC=0.75%
- Boiling point 50 C
- Corrosion except: Cr, Ni, Ti
- Polyethylene is resistive
- High blood:gas and fat:blood partition coefficient (induction slow, speed of recovery lengthened)
- Dose dependently decreases RR
- Heart muscle deprivation
- Bradycardia
- Increase CBF, CBV and CSF pressure
- Renal blood flow and GFR ↓
- Respiration depression (fast, superficial ventilation)
- Bronchorelaxant (last resort in patients with status asthmaticus)
- Striated muscles relaxes (not so heavy effect)
- Malignant hyperthermia (Metabolic acidosis, tachycardia, accelerated muscle contraction, hyperthermia)
- Relaxes uterus (good in case of prenatal manipulation (version))
- Halothan hepatitis (Metabolite trifluoroacethychloride trifluoroacethylates proteins → immune reaction)
- 80 % is excreted in unchanged form (20 % metabolized)
- Low cost!

Methoxyflurane

- Fluorinated ether
- High effectiveness and high lipid solubility
- Induction and recovery are slower than in case of halothan
- Cardiorespiratory depression
- Arrythmia provocation
- 50% is metabolized to fluorid
- Oxalate shows up in the urine
- Has a high extent of renal toxicity

Enflurane

- Rapid induction of general anaesthesia
- MAC=1.6 %
- Faster than methoxyflurane
- Almost no metabolization (2 % metabolized to fluoride ion → excreted by the kidney)
- Decreases HR, BP, TPR
- Can produce arrythmia
- Kidneys are not damaged, but fluoride can be toxic
- Can cause convulsions

Isoflurane FORANE

- Non-explosive, not flammable
- Non-toxic
- Blood:gas partition coeff is low 1.4 → Induction and recovery faster
- Resembling to enflurane but free of convulsion producing effect
- 99 % excreted in unchanged form
- 0.2 % metabolized by CYP2E1
- 1-2 % (MAC=1.15 %) for maintenance of anaesthesia,
- Expensive (because of the separation of enantimers)
- Concentration dependently decreases RR
- Increases HR
- Vasodilation everywhere esp. skin, muscle. Potent coronary vasodilator. (Coronary steal???)
- Attenuates baroreceptor function
- Concentration-dependent depression of ventilation (tidal volume ↓)
- Bronchodilator but airway irritant (coughing, laryngospasm)
- CBF ↑, Renal BF and GFR ↓
- Used widely

Desflurane SUPRANE

- No metabolism
- MAC: 6%
- Similar to isoflurane
- Potential for malignant hyperthermia

Sevoflurane SEVORANE

- Sevoflurane
  - For children
  - Waking is fast
  - can interact with the CO2 absorbant soda lime
  - Non-flammable, non-explosive
  - For children not-airway irritant
  - Exothermic interaction with the CO2 absorbant desiccated soda lime → airway burns, spontaneous ignition, explosion, fire
  - Desiccated (used) CO2 absorbent is dangerous → sevoflurane will liberate CO!
  - Low solubility → rapid induction, rapid recovery and ease in setting the required amount
  - 2-4 % is used, MAC: 1.8 %
  - Almost no metabolization
  - Concentration-dependent decrease in RR
  - Does not produce tachycardia!
  - Potent bronchodilator

Nitrogenium oxydulatum
Nitrous oxide (laughing gas)

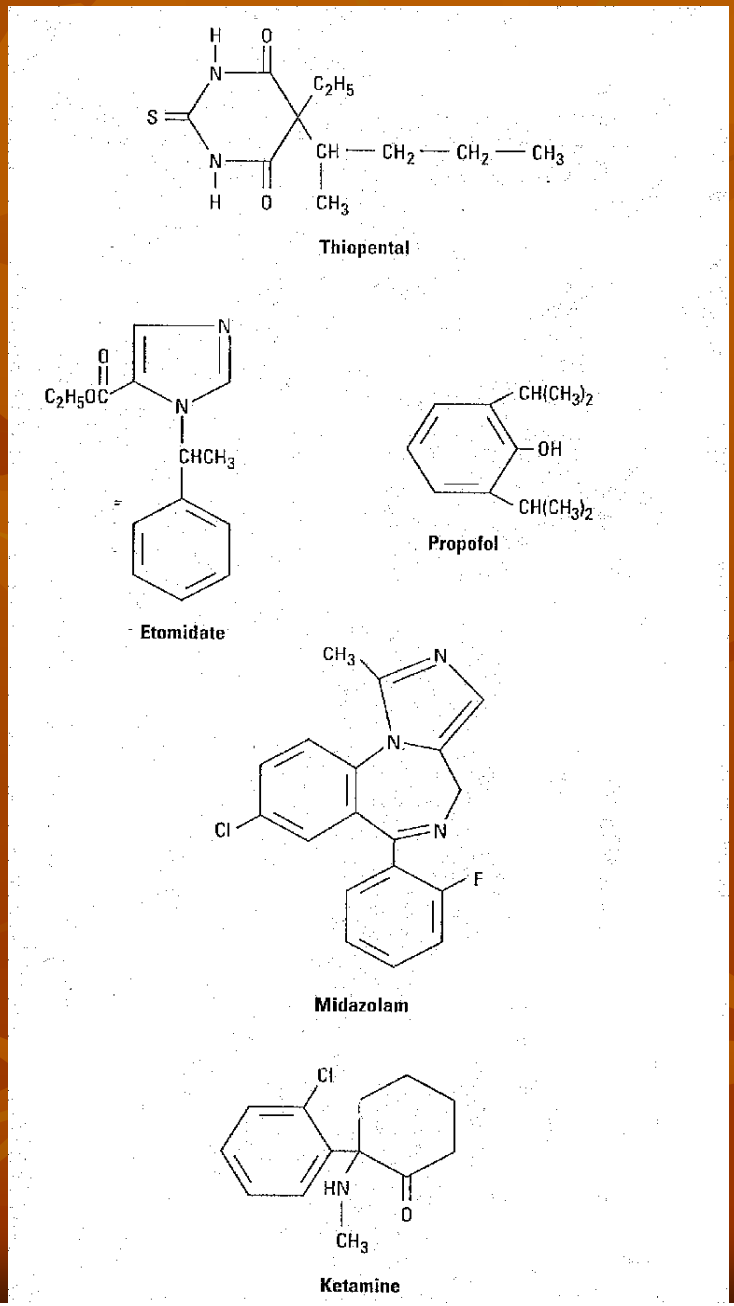
- Colorless
- Odorless
- Tasteless
- 75% N_2O and 25% O_2, MAC: 100% !!!
- Hallucinations
- Weak to use it alone
- Co will be oxidized in B_{12} – DNA synthesis inhibition, megalobalstic anemia, leucopenia (bone marrow depression), neuropathies
- Closed air cavities (pneumothorax) are filled by diffusion
- Diffusion hypoxia!!

Xenon

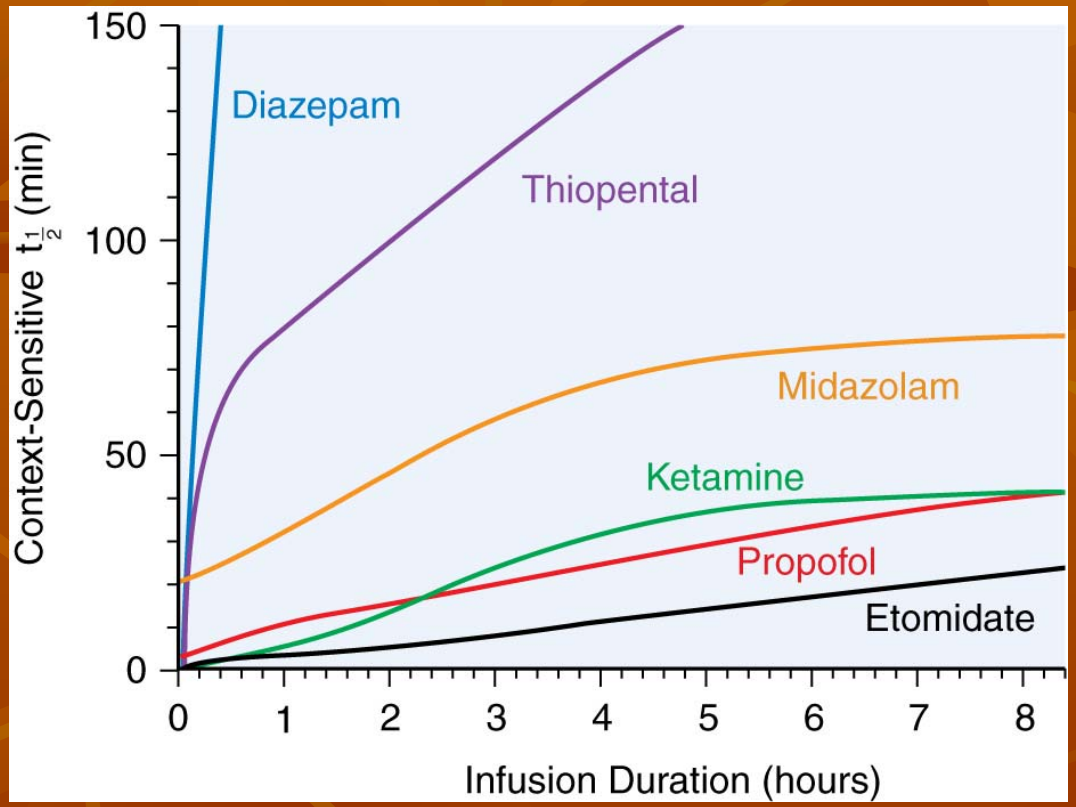
- almost the ideal general anaesthetic
- should not be used with rubber anaesthesia circuits
- has a high MAC value
- has the lowest blood:gas partition coefficient among inhalational anaesthetics
- Not approved in the US
- Very expensive
- Advantage: minimal cardiorespiratory side effects
- NMDA antagonist, TREK channel agonist

Intravenous Anesthetics

- Used in combination with Inhaled anesthetics to:
  - Supplement general anesthesia
  - Maintain general anesthesia
  - Provide sedation
  - Control blood pressure
  - Protect the brain



Context-Sensitive Half-Time

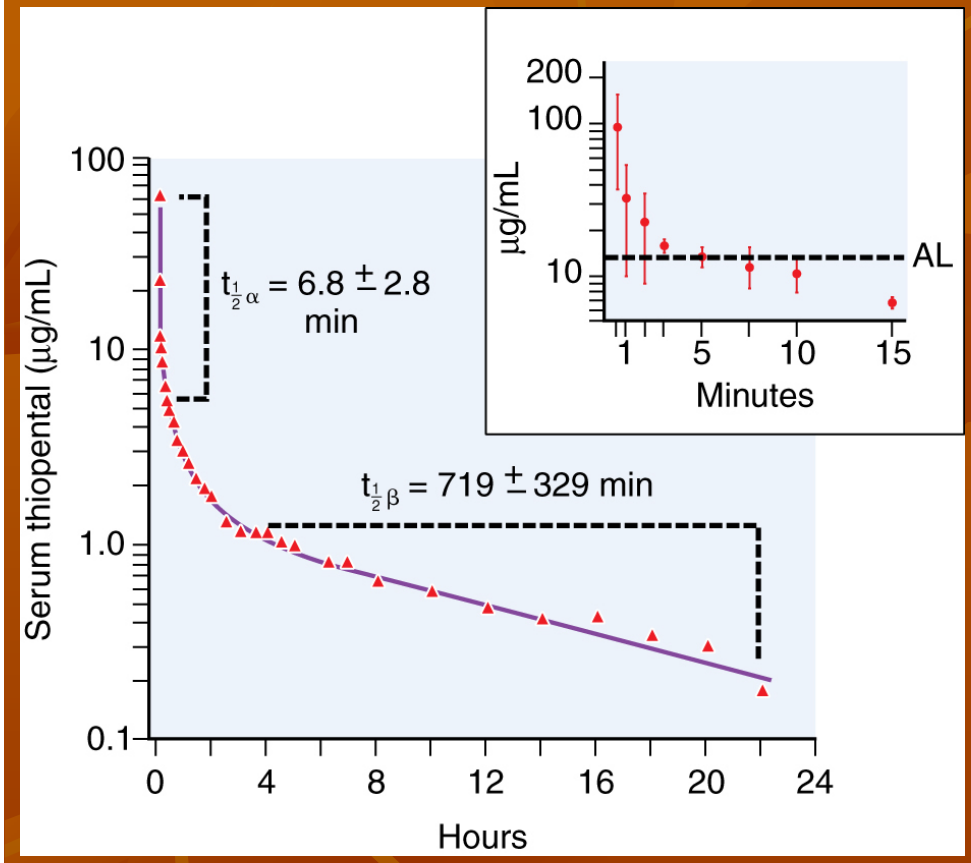


Complex interaction between:

the rate of redistribution of the drug

the amount of drug accumulated in fat

the drug's metabolic rate



Thiopental serum levels after a single intravenous induction dose. Thiopental serum levels after a bolus can be described by two time constants, t1/2α and t1/2β.The initial fall is rapid (t1/2α<10 min) and is due to redistribution of drug from the plasma and the highly perfused brain and spinal cord into less well-perfused tissues such as muscle and fat. During this redistribution phase, serum thiopental concentration falls to levels at which patients awaken (AL, awakening level; see inset—the average thiopental serum concentration in 12 patients after a 6-mg/kg intravenous bolus of thiopental). Subsequent metabolism and elimination is much slower and is characterized by a half-life (t1/2 β) of more than 10 hours. (Adapted with permission from Burch PG, and Stanski DR, The role of metabolism and protein binding in thiopental anesthesia. Anesthesiology, 1983, 58:146–152.

Table 19–2

Pharmacological Properties of Parenteral Anesthetics

DRUG	FORMULATION	IV INDUCTION DOSE (mg/kg)	MINIMAL HYPNOTIC LEVEL (μg/mL)	INDUCTION DOSE DURATION (min)	$t_{1/2}\beta$ (HOURS)	CL (mL·min^{-1}·kg^{-1})	PROTEIN BINDING (%)	V_{SS} (L/kg)
Thiopental	25 mg/mL in aqueous solution + 1.5 mg/mL Na_2CO_3; pH = 10–11	3-5	15.6	5-8	12.1	3.4	85	2.3
Methohexital	10 mg/mL in aqueous solution + 1.5 mg/mL Na_2CO_3; pH = 10–11	1-2	10	4-7	3.9	10.9	85	2.2
Propofol	10 mg/mL in 10% soybean oil, 2.25% glycerol, 1.2% egg PL, 0.005% EDTA or 0.025% Na-MBS; pH = 4.5–7	1.5-2.5	1.1	4-8	1.8	30	98	2.3
Etomidate	2 mg/mL in 35% PG; pH = 6.9	0.2-0.4	0.3	4-8	2.9	17.9	76	2.5
Ketamine	10, 50, or 100 mg/mL in aqueous solution; pH = 3.5–5.5	0.5-1.5	1	10-15	3.0	19.1	27	3.1

$t_{1/2}\beta$, β phase half-life; CL, clearance; V_{ss}, volume of distribution at steady state; EDTA, ethylenediaminetetraacetic acid; Na-MBS, Na-metabisulfite; PG, propylene glycol; PL, phospholipid.

Table 19–3

Some Pharmacological Effects of Parenteral Anesthetics[a]

DRUG	CBF	$CMRO_2$	ICP	MAP	HR	CO	RR	$\dot{V}_E$
Thiopental	---	---	---	-	+	-	-	--
Etomidate	---	---	---	0	0	0	-	-
Ketamine	++	0	++	+	++	+	0	0
Propofol	---	---	---	--	+	-	--	---

ABBREVIATIONS: CBF, cerebral blood flow; $CMRO_2$, cerebral oxygen consumption; ICP, intracranial pressure; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; RR, respiratory rate; $\dot{V}_E$, minute ventilation.

[a]Typical effects of a single induction dose in humans; *see* text for references. Qualitative scale from --- to +++ = slight, moderate, or large decrease or increase, respectively; 0 indicates no significant change.

Thiopenthal (Trapanal)

- Barbiturate
- Analgesic effectiveness is bad
- Respiratory depression
- Is used only for induction
- Excretion is too long
- Paravenous adm can cause necrosis
- Ia can cause vasospasm
- Contraindicated in acute intermittent prophyria and porphyria variegata

Other barbiturates:
Thiobutobarbital (Inactin)
Methohexital (Brietal)
Thiamylal (Surital)

Etomidate

- Faster metab than thiopenthal
- Involuntary movements occur during induction
- Postop vomitus can be observed
- Renal cortex is suppressed

Propanidid (Sombrevin)

- Onset 30 s
- Lasts for 5-6 min
- 0,5 g the starting dose
- Histamine is liberated

Ketamine (Calypsol)

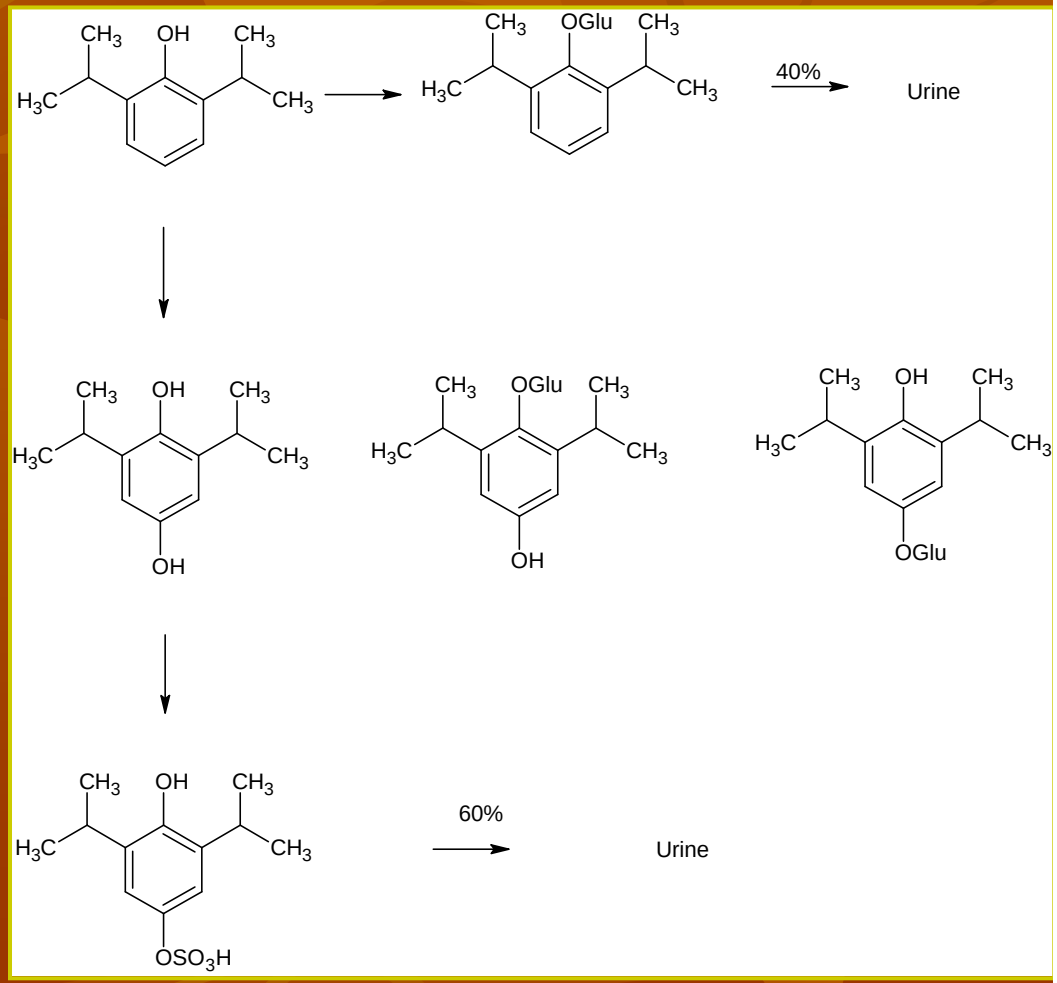
- Hallucinogenic
- For dissociative narcosis
- Muscle relaxant is necessary to administer
- Circulation is not influenced highly
- Spontaneous breath is maintained
- Blocks catecholamine reuptake

Mechanism of propofol (Diprivan)

- Inhibits the response to painful stimuli by interacting with **$beta_3$** subunit of $GABA_A$ receptor
- Sedative effects of Propofol mediated by the same $GABA_A$ receptor on the **$beta_2$** subunit
  - Indicates that two components of anesthesia can be mediated by $GABA_A$ receptor
- Action of Propofol
  - Positive modulation of inhibitory function of GABA through $GABA_A$ receptors

Metabolism of propofol

- Propofol is extensively metabolized
  - 88% of an administered dose appearing in the urine
- Eliminated by the hepatic conjugation of the inactive glucuronide metabolites which are excreted by the kidney
- Suitable for one-day surgery



Adverse effects of propofol

- Hypotension
- Arrhythmia
- Myocardial ischemia
  - Restriction of blood supply
- Confusion
- Rash
- Hyper-salivation
- Apnea

Midazolam (Dormicum)

- The onset of the effect is slow
- Recovery is slow
- Advantage: no cardiorespiratory derpessive effect

Anaesthetic Suppression of Physiological Response to Surgery