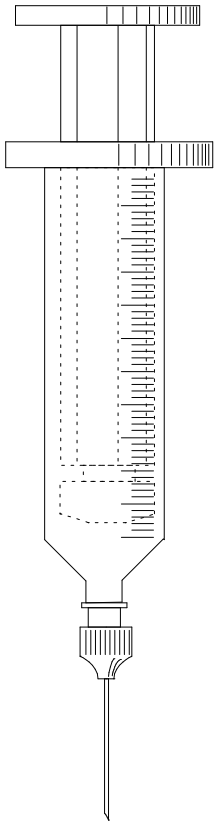
Intravenous anesthetics



Done by : Dr.Mohammad Abu Shihab

Types of IV anesthesia

- Use specific drugs for each component
  - **analgesia :**
    - To relave pain . Opioids (morphine , fentanyl,remifentanil …)
  - **hypnotics**:
    - Produce amnesia, and preferably unconsciousness, (propofol, midazolam, diazepam, thiopental, ketamine etomidate)
  - **Muscle relaxant**:
    - To relax muscle (succinyl choline , Rocuronium ,atracurium ..)

Definition

An agents that will induce a state of surgical anaesthesia in one arm brain circulation time

Function of intravenous anaesthetic agents

- induction of anaesthesia
- Maintenance of anaesthesia
- ICU/theatre sedation
- Status epilepticus

Pharmacokinetics

- Agent has to cross the BBB

- **Pharmacokinetics defines the relationships among drug dosing, drug concentration in body fluids and tissues, and time. It consists of four linked processes: absorption, distribution, biotransformation, and excretion.**

FACTOR	ACTION AFFECTED	DESCRIPTION
pKa	Onset	Lower pKa = more rapid onset of action, more RN molecules present to diffuse through nerve sheath, thus onset time is decreased
Lipid solubility	Anesthetic potency	Increased lipid solubility = increased potency
Protein binding	Duration	Increased protein binding allows anesthetic cations (RNH^+) to be more firmly attached to protein located at receptor sites, thus duration of action is increased
Tissue diffusibility	Onset	Increased diffusibility = decreased time of onset
Vasodilator activity	Anesthetic potency and duration	Greater vasodilator activity = increased blood flow to region = rapid removal of anesthetic molecules from injection site, thus decreased anesthetic potency and decreased duration

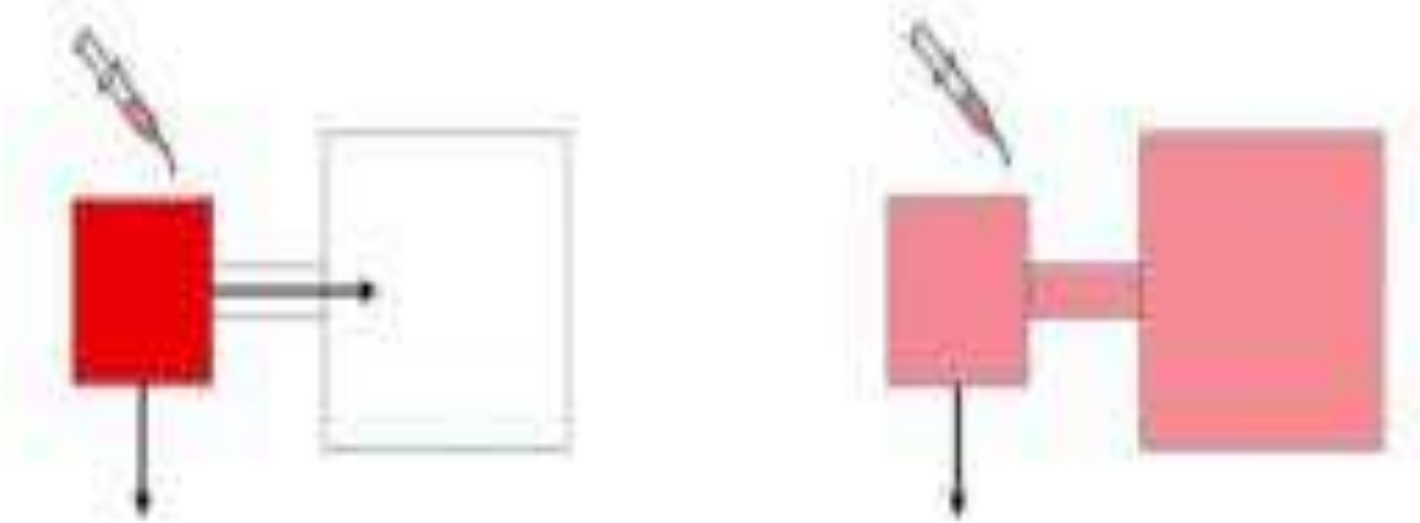
Handbook of Local Anesthesia, Stanley F. Malamed

Compartment Model

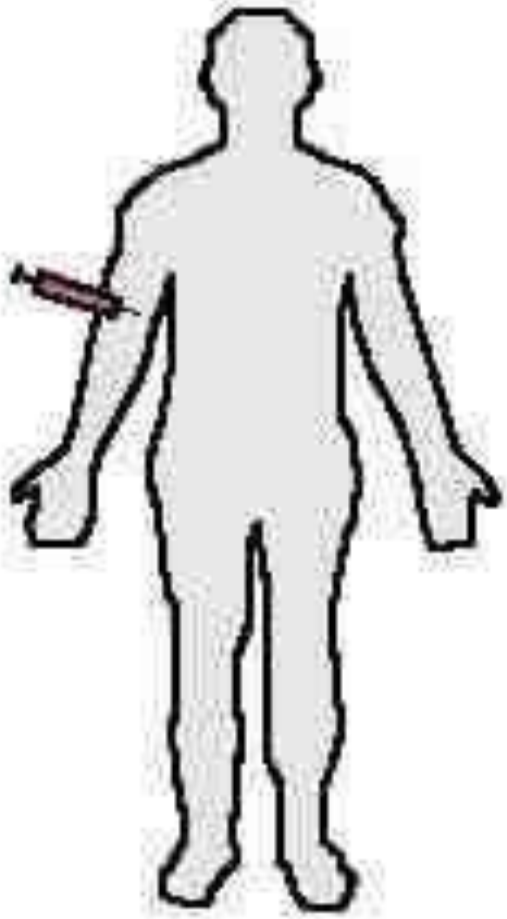
- Offers a simple way to characterize the distribution of drugs in the body
- Can be conceptualized as a group of tissues that posses similar pharmacokinetics (Central and peripheral compartments)
- Distribution phase vs. Elimination phase

Two-compartment models

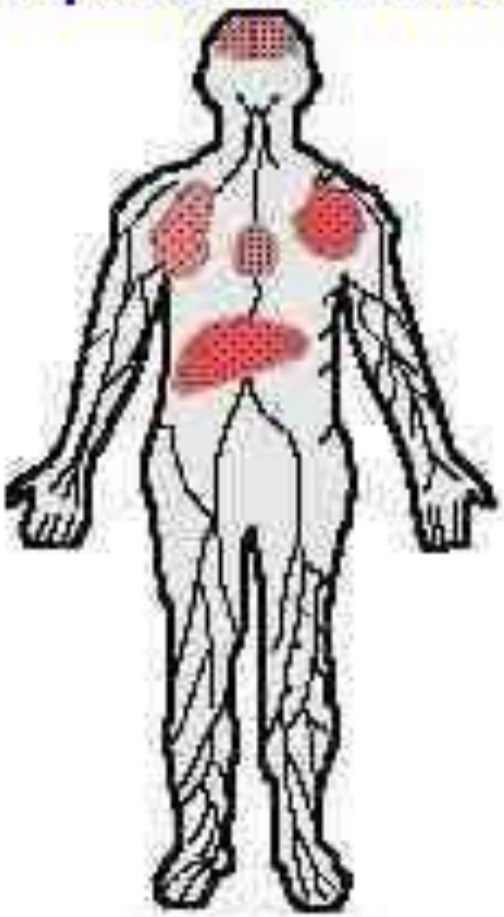
- Distribution to some parts of the distribution space takes time (not instantaneous)
- V_D becomes larger until equilibrium is reached



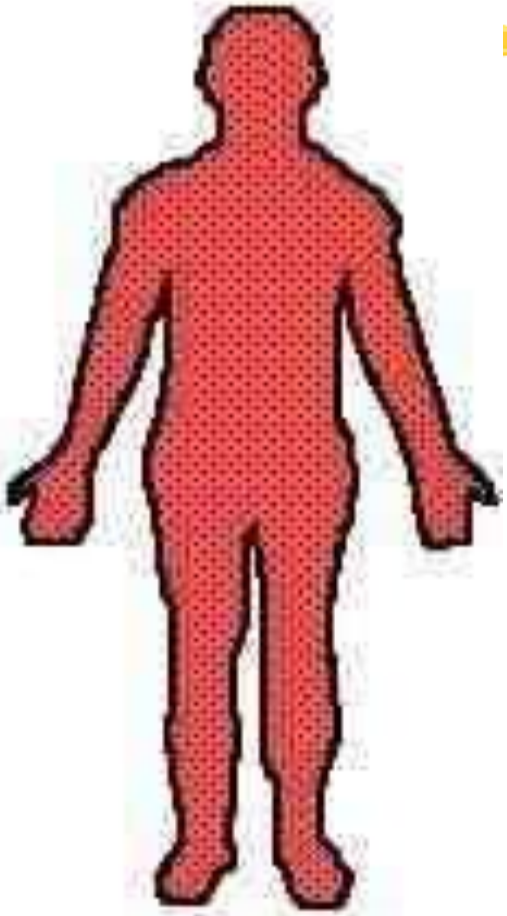
Two compartment model



Before Administration



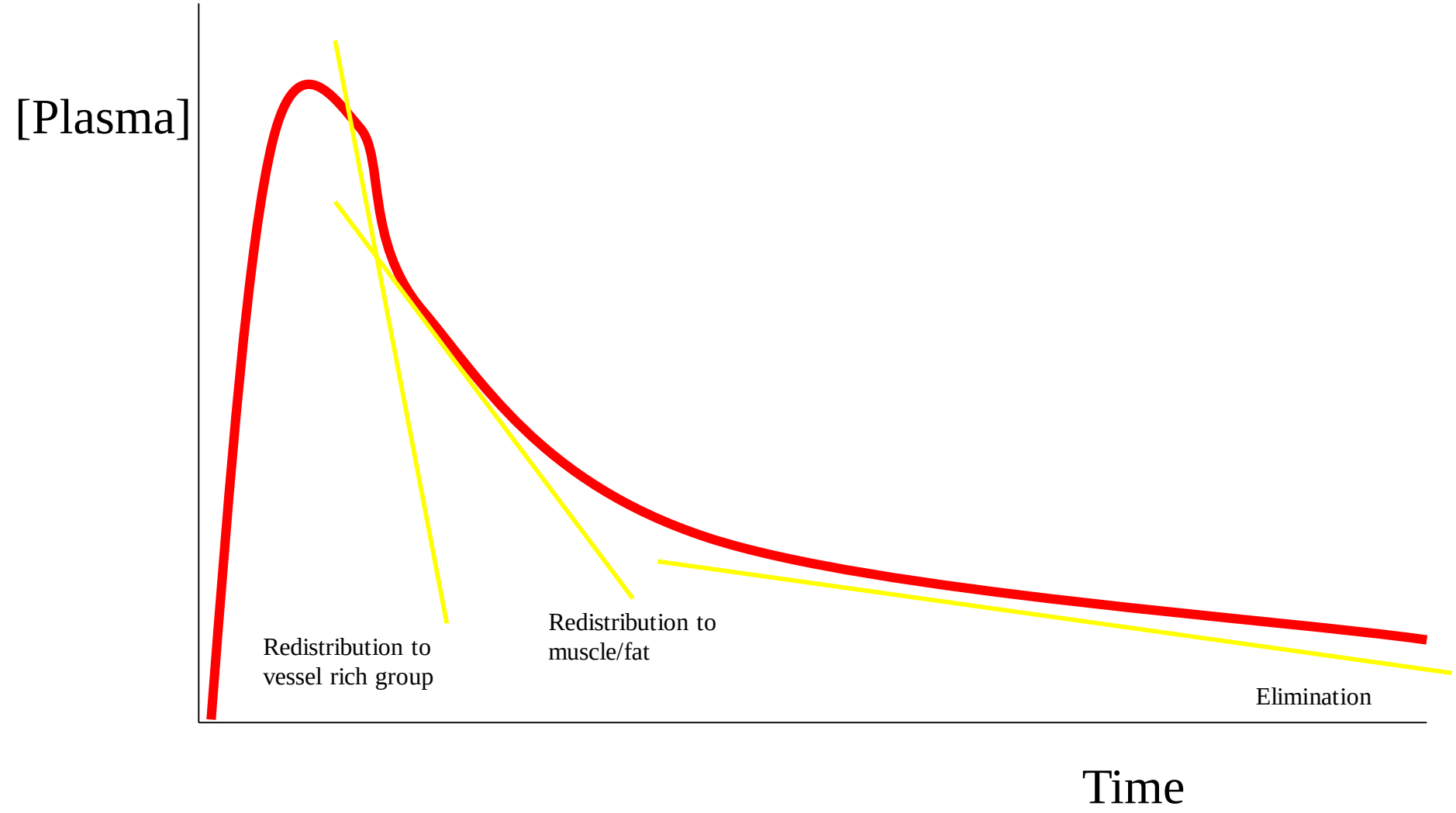
Immediately after Administration



After distribution equilibirum

Tissue Group	Composition	Body Mass (%)	Cardiac Output (%)
Vessel-rich	Brain, heart, liver, kidney, endocrine glands	10	75
Muscle	Muscle, skin	50	19
Fat	Fat	20	6
Vessel-poor	Bone, ligament, cartilage	20	0

Redistribution and elimination of intravenous anaesthetic agents

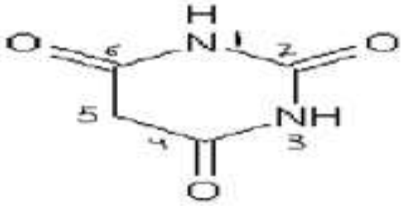


The ideal intravenous agent

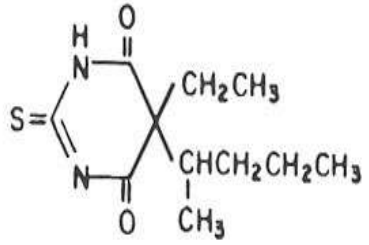
- Rapid onset
- Rapid recovery
- Analgesic
- No CVS/RS depression
- No emetic effects
- No excitatory phenomena
- No pain on injection
- Safe if injected intra-arterially
- None toxic to other organs
- No histamine release
- No allergic reaction

Barbiturates

Barbiturates



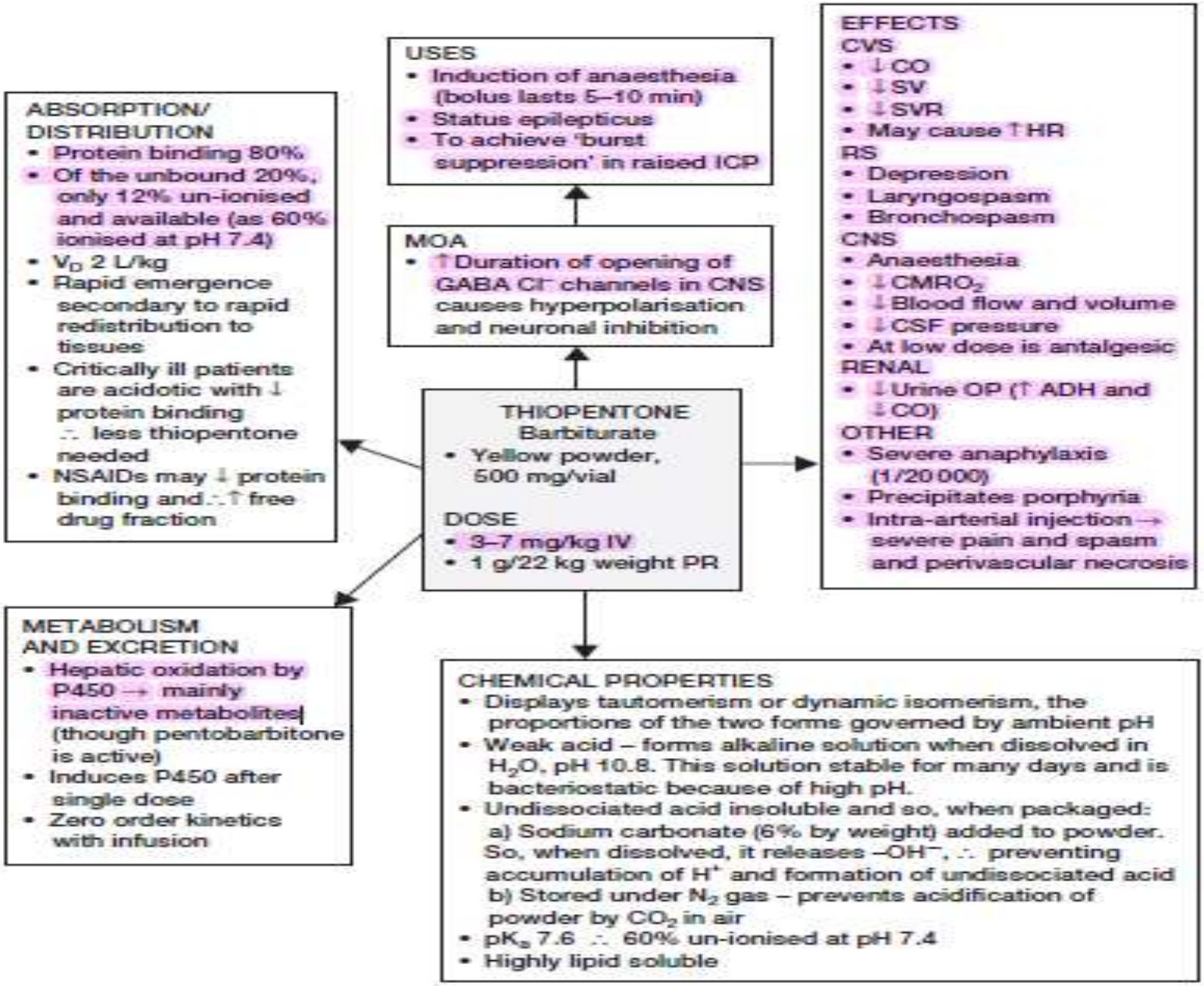
- Derived from barbituric acid
- Prepared as sodium salts
- Highly alkaline (pH : 10.5)
- Available as racemic mixtures



Thiopental

- Oxybarbiturates → methohexital
- Thiobarbiturates → thiopental, thiamylal

Thiopentone



Thiopental

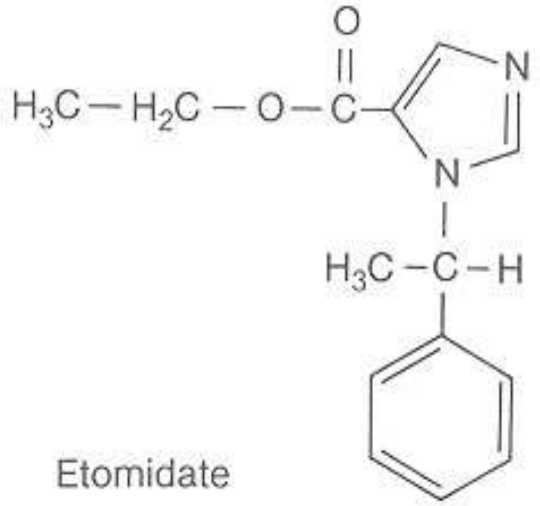
- Adverse effects
  - Hypotension
  - Respiratory depression
  - Laryngeal spasm
  - Brochospasm
  - Allergic reactions (1 in 14,000)
  - Extravasation tissue necrosis
  - Intraarterial injection
  - Thrombophlebitis

- Contraindications
  - Airway obstruction
  - Porphyria
  - Hypersensitivity

Etomidate

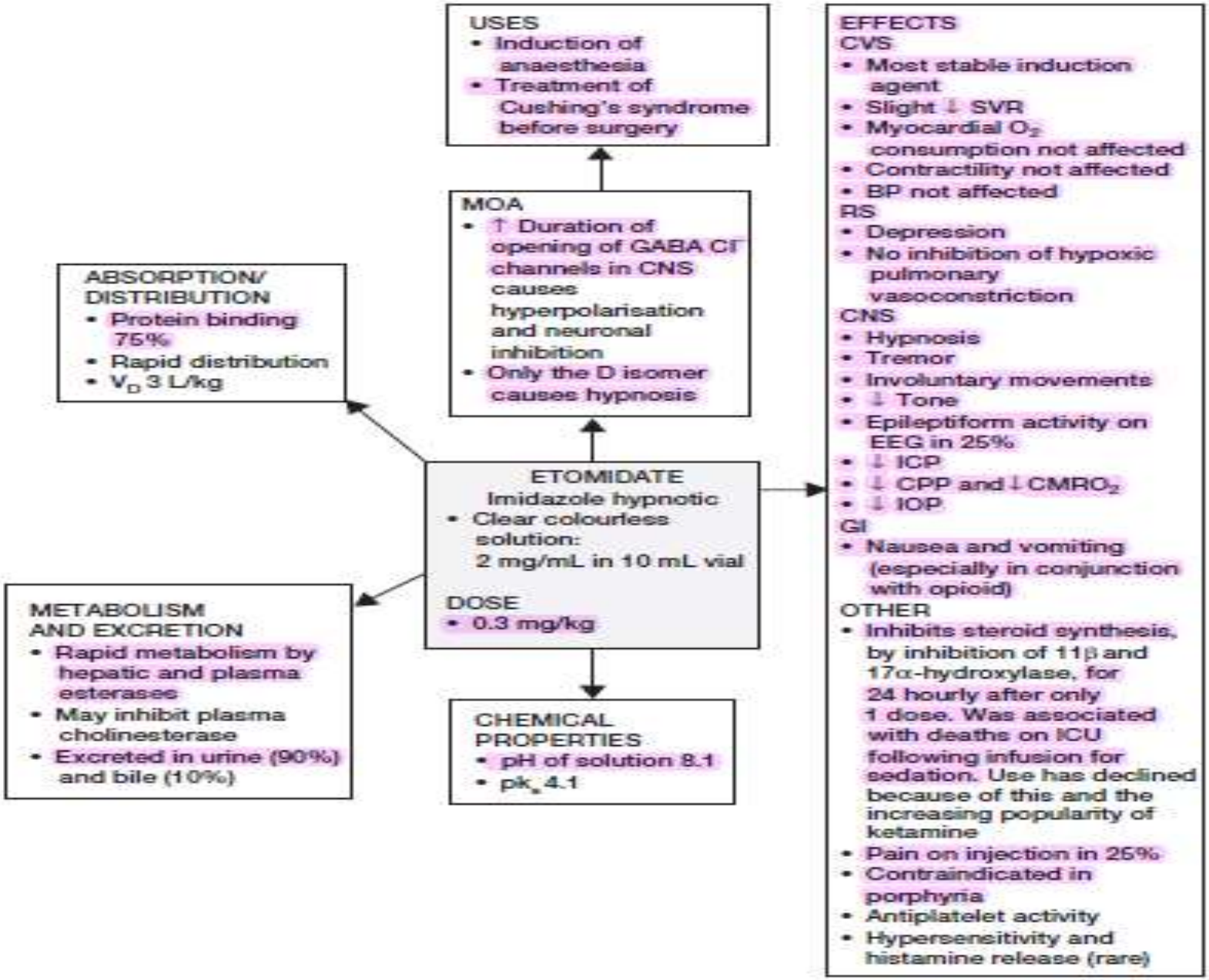
Etomidate

- Contains carboxylated imidazole ring which provides water solubility at physiological pH
- Depresses the reticular activating system and mimics the inhibitory effects of GABA
- Binds to subunit of GABA type A receptor increasing its affinity to GABA
- Induction dose: 0.2-0.4 mg/kg



Etomidate

Etomidate


USES
• Induction of anaesthesia
• Treatment of Cushing's syndrome before surgery
MOA
• ↑ Duration of opening of GABA Cl⁻ channels in CNS causes hyperpolarisation and neuronal inhibition
• Only the D isomer causes hypnosis
ABSORPTION/ DISTRIBUTION
• Protein binding 75%
• Rapid distribution
• V_D 3 L/kg
ETOMIDATE
Imidazole hypnotic
• Clear colourless solution: 2 mg/mL in 10 mL vial
DOSE
• 0.3 mg/kg
METABOLISM AND EXCRETION
• Rapid metabolism by hepatic and plasma esterases
• May inhibit plasma cholinesterase
• Excreted in urine (90%) and bile (10%)
CHEMICAL PROPERTIES
• pH of solution 8.1
• pk_a 4.1
EFFECTS
CVS
• Most stable induction agent
• Slight ↓ SVR
• Myocardial O_2 consumption not affected
• Contractility not affected
• BP not affected
RS
• Depression
• No inhibition of hypoxic pulmonary vasoconstriction
CNS
• Hypnosis
• Tremor
• Involuntary movements
• ↓ Tone
• Epileptiform activity on EEG in 25%
• ↓ ICP
• ↓ CPP and ↓ $CMRO_2$
• ↓ IOP
GI
• Nausea and vomiting (especially in conjunction with opioid)
OTHER
• Inhibits steroid synthesis, by inhibition of 11β and 17α-hydroxylase, for 24 hourly after only 1 dose. Was associated with deaths on ICU following infusion for sedation. Use has declined because of this and the increasing popularity of ketamine
• Pain on injection in 25%
• Contraindicated in porphyria
• Antiplatelet activity
• Hypersensitivity and histamine release (rare)

Side effects

- May activate seizure, extrapyramidal activity .
- Pain on injection
- Adrenocortical suppression
- Allergic reactions

Ketamine

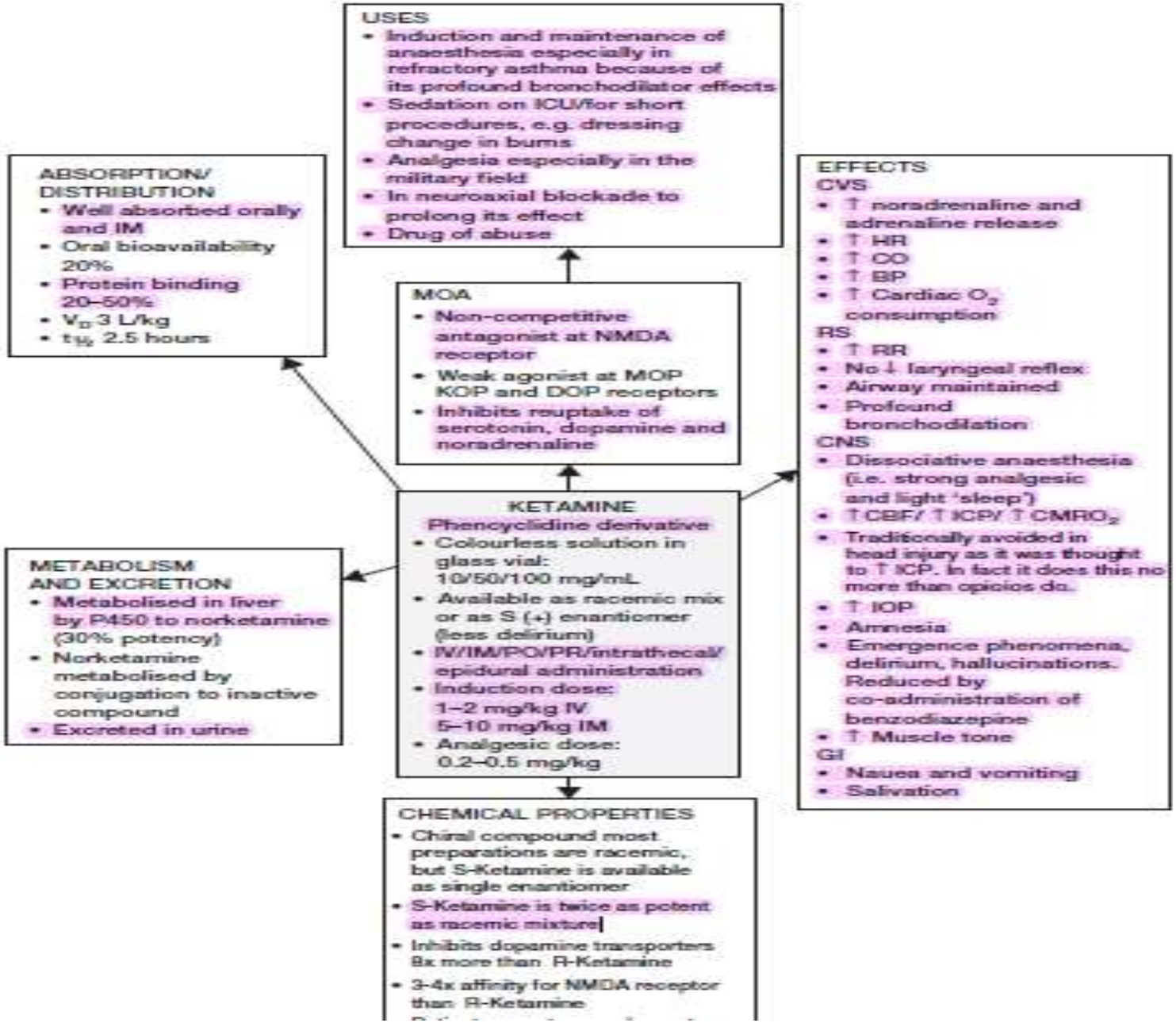
Ketamine

- Has multiple effects through the CNS including blocking polysynaptic reflexes in the spinal cord and inhibiting neurotransmitter effects in selected areas of the brain
- Ketamine dissociates the thalamus from the limbic cortex (dissociative anesthesia)

  Causes the pt to appear concious but unable to process or respond to sensory input .
- N-methyl-D-aspartae receptor antagonist
- Can cause hallucinogenic effects and nightmares
- Dose : Induction IV 1-2 mg/kg, IM 3-5 mg/kg

Ketamine

Ketamine

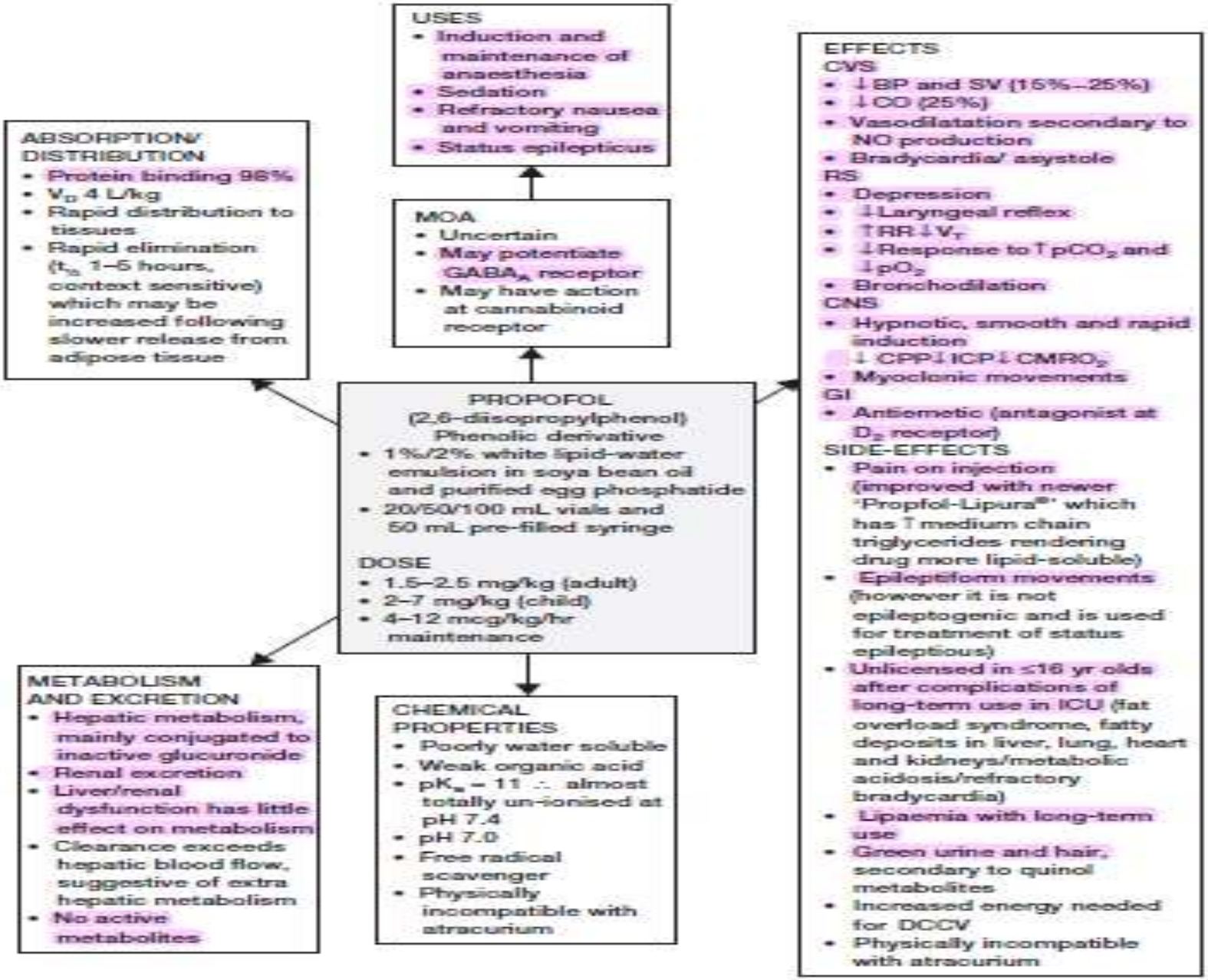

USES
• Induction and maintenance of anaesthesia especially in refractory asthma because of its profound bronchodilator effects
• Sedation on ICU/for short procedures, e.g. dressing change in burns
• Analgesia especially in the military field
• In neuroaxial blockade to prolong its effect
• Drug of abuse
ABSORPTION/ DISTRIBUTION
• Well absorbed orally and IM
• Oral bioavailability 20%
• Protein binding 20–50%
• V_D 3 L/kg
• $t_{1/2}$ 2.5 hours
MOA
• Non-competitive antagonist at NMDA receptor
• Weak agonist at MOP KOP and DOP receptors
• Inhibits reuptake of serotonin, dopamine and noradrenaline
EFFECTS
CVS
• ↑ noradrenaline and adrenaline release
• ↑ HR
• ↑ CO
• ↑ BP
• ↑ Cardiac O_2 consumption
RS
• ↑ RR
• No ↓ laryngeal reflex
• Airway maintained
• Profound bronchodilation
CNS
• Dissociative anaesthesia (i.e. strong analgesic and light 'sleep')
• ↑ CBF/ ↑ ICP/ ↑ $CMRO_2$
• Traditionally avoided in head injury as it was thought to ↑ ICP. In fact it does this no more than opioids do.
• ↑ IOP
• Amnesia
• Emergence phenomena, delirium, hallucinations. Reduced by co-administration of benzodiazepine
• ↑ Muscle tone
GI
• Nausea and vomiting
• Salivation
KETAMINE
Phencyclidine derivative
• Colourless solution in glass vial: 10/50/100 mg/mL
• Available as racemic mix or as S (+) enantiomer (less delirium)
• IV/IM/PO/PR/intrathecal/ epidural administration
• Induction dose: 1–2 mg/kg IV 5–10 mg/kg IM
• Analgesic dose: 0.2–0.5 mg/kg
METABOLISM AND EXCRETION
• Metabolised in liver by P450 to norketamine (30% potency)
• Norketamine metabolised by conjugation to inactive compound
• Excreted in urine
CHEMICAL PROPERTIES
• Chiral compound most preparations are racemic, but S-Ketamine is available as single enantiomer
• S-Ketamine is twice as potent as racemic mixture
• Inhibits dopamine transporters 8x more than R-Ketamine
• 3-4x affinity for NMDA receptor than R-Ketamine

Propofol

Alkylphenols

- Facilitate inhibitory neurotransmitters mediated by GABA
- Propofol (2,6-diisopropylphenol) consist of phenol ring with two isopropyl groups attached
- Altering the side chain of this alkylphenol influences potency, induction and recovery characteristics
- It can attenuate upper airway reflexes.
- Formulation can support bacterial growth (soybean oil, glycerol, and egg lecithin)
- Dose : induction IV 1.5-2.5 mg/kg
- Not water soluble

Propofol


USES
• Induction and maintenance of anaesthesia
• Sedation
• Refractory nausea and vomiting
• Status epilepticus
ABSORPTION/ DISTRIBUTION
• Protein binding 96%
• V_D 4 L/kg
• Rapid distribution to tissues
• Rapid elimination ($t_{½}$ 1–5 hours, context sensitive) which may be increased following slower release from adipose tissue
MOA
• Uncertain
• May potentiate $GABA_A$ receptor
• May have action at cannabinoid receptor
EFFECTS
CVS
• ↓BP and SV (15%–25%)
• ↓CO (25%)
• Vasodilatation secondary to NO production
• Bradycardia/ asystole
RS
• Depression
• ↓Laryngeal reflex
• ↑RR↓V_T
• ↓Response to ↑pCO_2 and ↓pO_2
• Bronchodilation
CNS
• Hypnotic, smooth and rapid induction
↓ CPP↓ ICP↓ $CMRO_2$
• Myoclonic movements
GI
• Antiemetic (antagonist at D_2 receptor)
SIDE-EFFECTS
• Pain on injection (improved with newer "Propfol-Lipura®" which has ↑ medium chain triglycerides rendering drug more lipid-soluble)
• Epileptiform movements (however it is not epileptogenic and is used for treatment of status epilepticus)
• Unlicensed in ≤16 yr olds after complications of long-term use in ICU (fat overload syndrome, fatty deposits in liver, lung, heart and kidneys/metabolic acidosis/refractory bradycardia)
• Lipaemia with long-term use
• Green urine and hair, secondary to quinol metabolites
• Increased energy needed for DCCV
• Physically incompatible with atracurium
PROPOFOL
(2,6-diisopropylphenol)
Phenolic derivative
• 1%/2% white lipid-water emulsion in soya bean oil and purified egg phosphatide
• 20/50/100 mL vials and 50 mL pre-filled syringe
DOSE
• 1.5–2.5 mg/kg (adult)
• 2–7 mg/kg (child)
• 4–12 mcg/kg/hr maintenance
METABOLISM AND EXCRETION
• Hepatic metabolism, mainly conjugated to inactive glucuronide
• Renal excretion
• Liver/renal dysfunction has little effect on metabolism
• Clearance exceeds hepatic blood flow, suggestive of extra hepatic metabolism
• No active metabolites
CHEMICAL PROPERTIES
• Poorly water soluble
• Weak organic acid
• pK_a – 11 ∴ almost totally un-ionised at pH 7.4
• pH 7.0
• Free radical scavenger
• Physically incompatible with atracurium

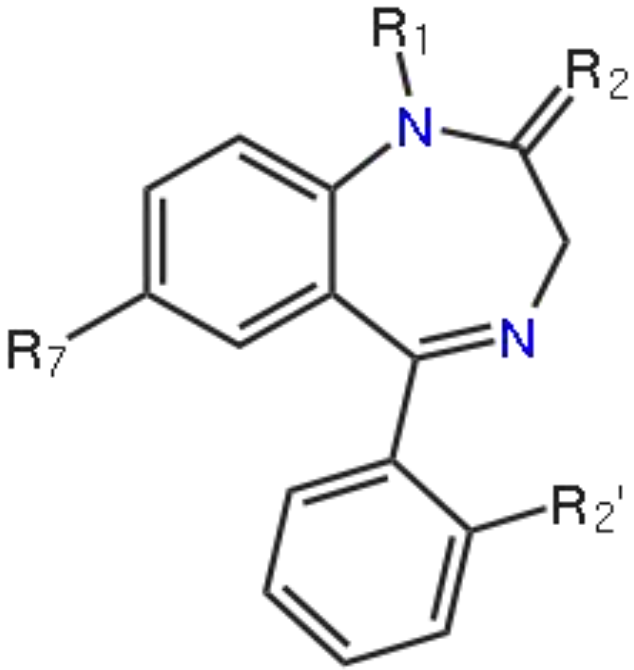
Side effects

- Allergic reactions
- Lactic acidosis (Propofol infusion syndrome)
- Bacterial growth
- Pain on injection

Benzodiazepines

Benzodiazepines

- Binding to receptors enhances the inhibitory effects of various neurotransmitters (GABA) in the CNS mainly in the cortex
- Chemical structure includes a benzene ring and a 7-member diazepine ring, substitution at various positions on these rings affect potency and biotransformation
- Flumazenil is a specific benzodiazepine-receptor antagonist that effectively reverses most of the CNS effect



Absorption

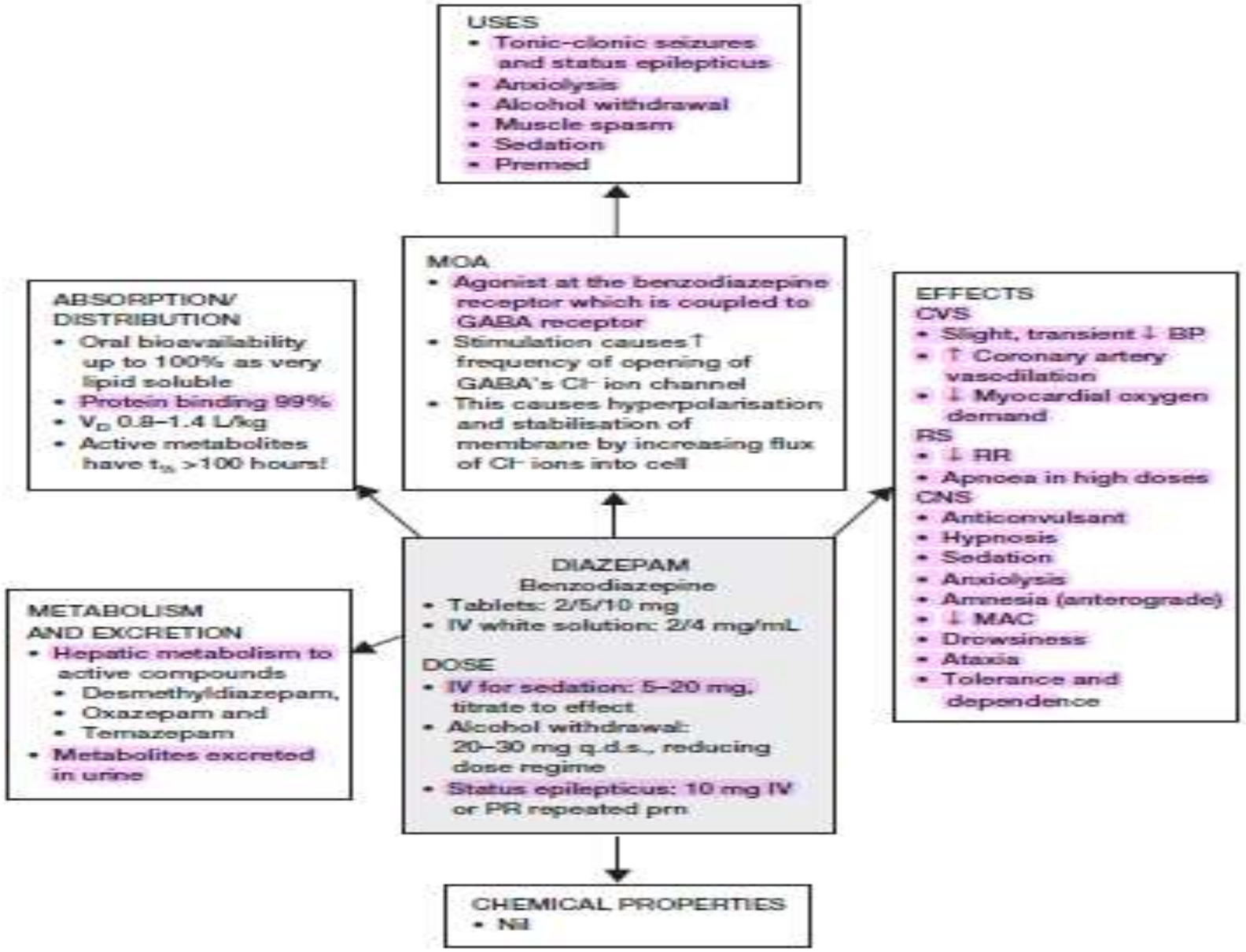
- Administered orally, IM and IV for sedation or induction of GA
- Diazepam and Lorazepam well absorbed from GI tract, peak plasma level in 1-2 h respectively
- Dose Midazolam : premedication IM 0.07-0.15 mg/kg, sedation IV 0.01-0.1 mg/kg, Induction IV 0.1-0.4 mg/kg

Distribution

- Diazepam is lipid soluble and rapidly cross the blood brain barrier.
- Redistribution is rapid for benzodiazepines (3-10 min)
- Highly protein bound (90-98%)

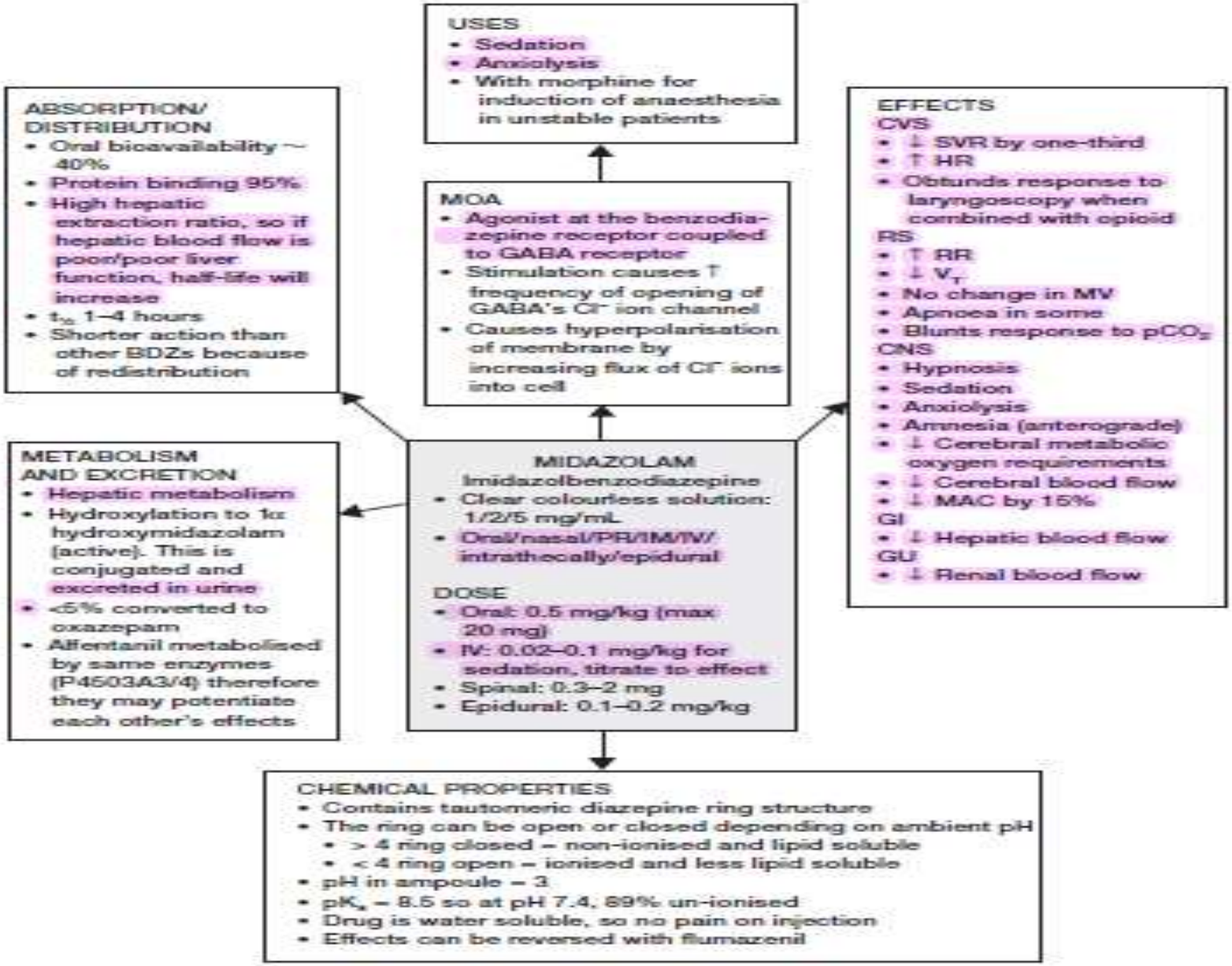
BENZODIAZEPINES

Diazepam



BENZODIAZEPINE

Midazolam



Agent	Cardiovascular		Respiratory		Cerebral		
	HR	MAP	Vent	B'dil	CBF	$CMRO_2$	ICP
Barbiturates							
Thiopental	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Thiamylal	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Methohexital	↑↑	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Benzodiazepines							
Diazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Lorazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Midazolam	↑	↓↓	↓↓	0	↓↓	↓↓	↓↓
Ketamine	↑↑	↑↑	↓	↑↑↑	↑↑↑	↑	↑↑↑
Etomidate	0	↓	↓	0	↓↓↓	↓↓↓	↓↓↓
Propofol	0	↓↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓

Properties of Intravenous Anesthetic Agents

Drug	Induction and Recovery	Main Unwanted Effects	Notes
thiopental	Fast onset (accumulation occurs, giving slow recovery) Hangover	Cardiovascular and respiratory depression	Used as induction agent declining. Decreases cerebral blood flow and O2 consumption. Injection pain
etomidate	Fast onset, fairly fast recovery	Excitatory effects during induction and recovery, **Adrenocortical suppression**	Less cardiovascular and respiratory depression than with thiopental, Injection site pain
propofol	Fast onset, very fast recovery	Cardiovascular and respiratory depression. Pain at injection site.	Most common induction agent. Rapidly metabolized; possible to use as continuous infusion. Injection pain. Antiemetic
ketamine	Slow onset, after-effects common during recovery	**Psychotomimetic effects** following recovery, Postoperative nausea, vomiting and salivation	Produces good **analgesia** and amnesia. No injection site pain
midazolam	Slower onset than other agents	Minimal CV and respiratory effects.	Little respiratory or cardiovascular depression. No injection pain. Good amnesia.

THANK YOU