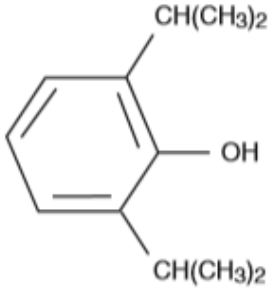
IV Anesthesia

R1 Soravish Sirilertworakul
Ekasak Chantrapannik, M.D.

1. Propofol

Propofol : Chemical Structure

- Alkylphenol compound-insoluble in aqueous solution, highly lipid soluble
- Oil at room temperature, insensitive to light, pH about 7
- Egg lecithin emulsion formulation
- Microbial growth
- Preparation : 1%, 2% Propofol



Propofol : Mechanism

- Sedative
  - enhancing GABA-induced chloride current through its binding to ß subunit of the GABAA receptor (alpha and gamma)
  - directly activate GABAA receptor channel
  - inhibit acetylcholine release in the hippocampus and prefrontal cortex
- Analgesia
  - NMDA receptor antagonists

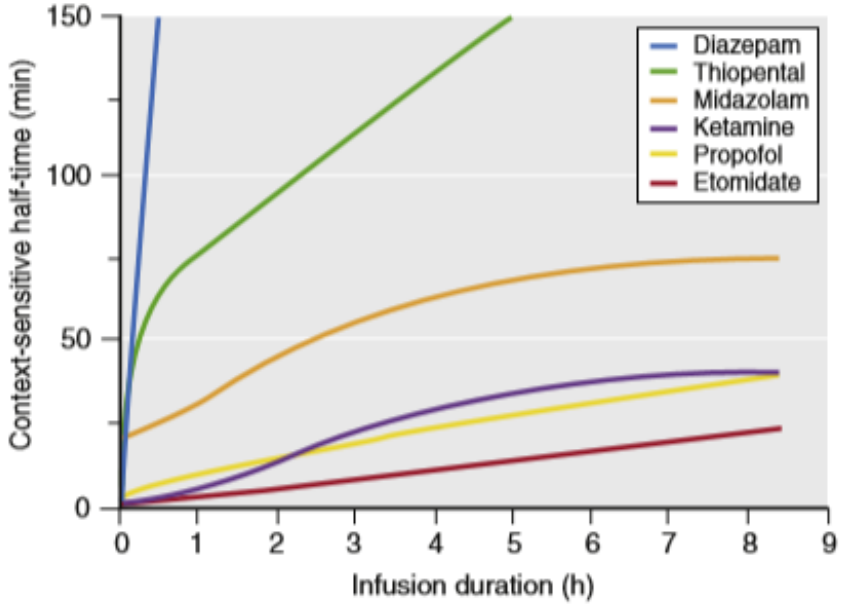
Propofol : Mechanism

- GABAA and glycine receptors in spinal cord
- Antiemetics
  - ↑ Serotonin in area of postrema
- Sense of well-being
  - ↑ Dopamine concentration in nucleus accumbens

Propofol : Pharmacokinetic

- Three compartment models
  - Initial distribution t1/2 2-8 mins
  - Slow distribution t1/2 30-70 mins
  - Elimination t1/2 4-7 hrs

- Low Context-sensitive half-time (at 8 hrs is less than 40 minutes)

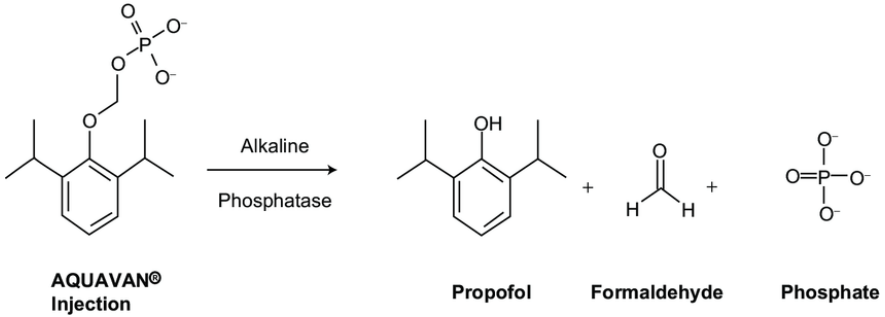


Propofol : Pharmacokinetic

- Metabolism : oxidized, conjugated with glucuronic acid at liver and excreted by kidney
- High hepatic extraction ratio
- Extrahepatic metabolism : renal (30%), lung (20-30%)
- CYP 3A4 Inhibitors

Fospropofol : Pharmacokinetic

- Prodrug of propofol
- Fospropofol 1.86 mg = Propofol 1 mg
- Onset 4-8 min



AQUAVAN®
Injection

Propofol **Formaldehyde** **Phosphate**

Metabolized by alkaline phosphatase to Propofol, Formaldehyde, Phosphate

Propofol : Pharmacokinetic

Decrease dose

- Elderly : increase drug sensitivity, central compartment, clearance ↓
- Pregnancy : prolonging elimination
- Co-administration drug e.g. midazolam, fentanyl
- Low cardiac output

Increase dose

- Pediatrics
- High cardiac output

Propofol : Pharmacodynamic (CNS)

- CNS depression, EEG suppression
- Cerebral metabolism (CMRO2) ↓, cerebral blood flow ↓(metabolic coupling), ICP ↓
- IOP ↓
- Anti-convulsant
- Controversial neuroprotection

Propofol : Pharmacodynamic (CVS)

- Direct negative inotropic effect
- Sympathetic outflow ↓
- vasodilation
- Depress Baroreceptor reflex
- BP ↓, CO ↓, HR ↔
- Atropine responsive ↓

Propofol : Pharmacodynamic (RS)

- RS depression (Central RS at medulla)
- TV ↓, RR ↑ (100 mcg/kg/min), RR ↔ (200 mcg/kg/min)
- Depress laryngeal/tracheal reflexes
- Bronchodilation

Propofol : Pharmacodynamic (Other)

- No effect on Liver/Kidney function
- Anti-emetics
- ↓ Peritus in Spinal opioid

Propofol : Clinical uses

- Induction dose: 1-2.5 mg/kg IV
  - Pediatrics : 2-3 mg/kg
  - Elderly : 1-1.75 mg/kg
- Maintenance of GA : 50-150 mcg/kg/mi IV (with opoid or N2O)
- Sedation : 25-75 mcg/kg/min

Propofol : Clinical uses

- TCI model : March, Schnider
- Blood levels for
  - Loss of consciousness 2.5-4.5 mcg/ml
  - Required for surgery 2.5-8.0 mcg/ml
  - Awakening 1.6 mcg/ml

Propofol : Clinical uses

- Antiemetic :
  - 10-20 mg IV, 10 mcg/kg/min
- Status epilepticus :
  - 2 mg/kg IV then 5-10 mg/kg/hr until stable then 1-3 mg/kg/hr

Propofol : Side effects

- Pain on injection
- Myoclonus
- Apnea
- Hypotension
- Propofol infusion syndrome (PRIS)

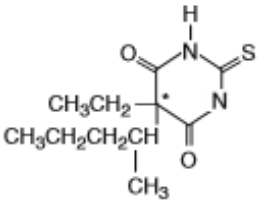
Propofol infusion syndrome (PRIS)

- Infusion of propofol > 4 mg/kg/h for > 48 hrs
- Clinical features : acute refractory bradycardia → Asystole, Heart failure, Rhabdomyolysis, Hepatomegaly
- Lab : Hypertriglyceridemia, Hyperkalemia, Metabolic acidosis, AKI
- Risk factors : Poor oxygen delivery, sepsis, cerebral injury
- Predisposing factors : genetic disorders (impairing fatty metabolism), low carbohydrate supply

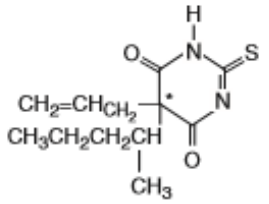
2. Barbiturates

Barbiturates : Chemical Structure

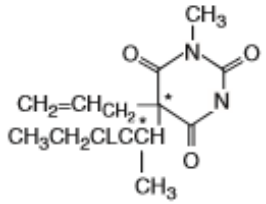
- Derivatives of Barbituric acid
- 2 major classes :
  - Oxybarbiturates
  - Thiobarbiturates



Thiopental



Thiamylal



Methohexital

Barbiturates : Chemical Structure

- Sodium salt reconstitution with water, 5%Glucose, NSS
- Cannot be reconstituted with acid solution e.g. (Formation of precipitated)
    - Ringer lactate solution
    - Atracurium
    - Rocuronium
    - Midazolam
    - Dopamine

Barbiturates : Mechanism

- Enhancement of synaptic action of inhibitory neurotransmitter by binding with GABA receptors
    - Decrease rate of dissociation of GABA
    - Direct activation of Cl channels
- Hyperpolarization of post-synaptic cell

Barbiturates : Mechanism

- Blockade synaptic actions of excitatory neurotransmitters
  - Inhibit glutamate and acetylcholine
  - Glutaminergic-NMDA system (extracellular glutamate and NMDA-gated currents)

Barbiturates : Pharmacokinetic

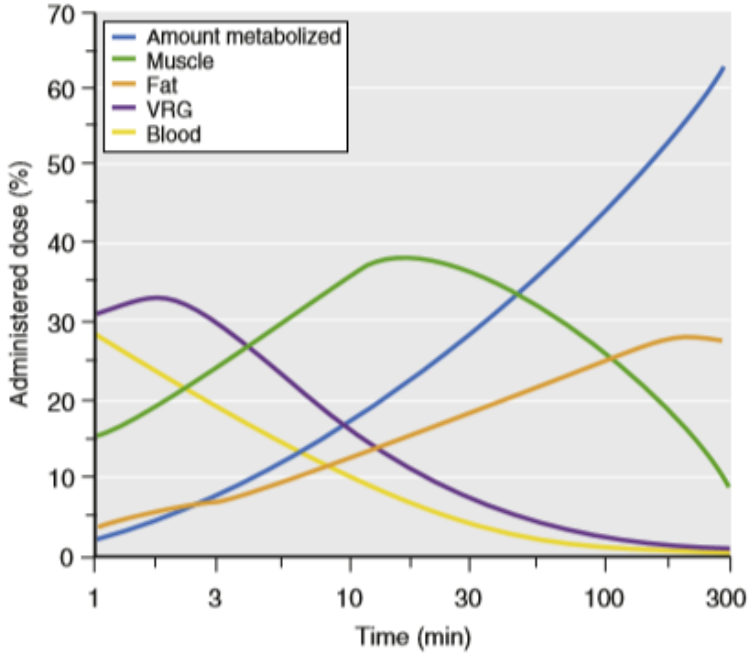
- Highly lipid soluble → rapid onset = 30-60 sec (one arm-brain circulation)
- Redistribution = 5-8 min → Duration of Induction dose
- Weak acid ; pKa = 7.6
- Protein bound 85%

Barbiturates : Pharmacokinetic

- Thiopental metabolism
  - Low hepatic extraction ratio = 0.15
  - Low-dose : Oxidation, N-dealkylation, Desulfuration at C2 at Liver -> Hydroxythiopental
  - First-order kinetic

- High-dose : Desulfuration -> Pentobarbital
  - Zero-order kinetic
  - Not suitable for prolong infusion

Barbiturates : Pharmacokinetic



Barbiturates : Pharmacokinetic

- Methohexital metabolism
  - Intermediate hepatic extraction ratio (0.5)
  - Oxidation and N-dealkylation at Liver -> Inactive hydroxy derivatives

Barbiturates : Pharmacokinetic

Decrease dose

- Elderly : decrease Vd, CO, increase drug sensitivity
- Pregnancy : prolonging elimination
- Premedication

Increase dose

- Pediatrics
- Chronic alcoholism

Barbiturates : Pharmacodynamic (CNS)

- Dose-dependent CNS depression
- EEG suppression
- Cerebral metabolism (CMRO2) ↓, cerebral blood flow ↓(metabolic coupling), ICP ↓
- IOP ↓
- Neuroprotection (focal ischemia)
- Anti-convulsant

Barbiturates : Pharmacodynamic (CVS)

- Direct negative inotropic effect
- Sympathetic outflow ↓
- Vasodilation
- Slightly depress Baroreceptor reflex
- BP ↓, CO ↓, HR ↑
- Prolonged QT interval, flatten T waves (caution in HD, Cirrhosis)

Barbiturates : Pharmacodynamic (RS)

- RS depression (Central RS at medulla)
- TV ↓, RR ↑
- “Double apnea”
- Depress laryngeal/tracheal reflexes less than propofol (Laryngo/bronchospasm Rx. NMBD)
- + Histamine

Barbiturates : Pharmacodynamic (Renal)

- Renal blood flow ↓ → GFR ↓, Oliguria
- Prophylaxis by adequate hydration, BP control

Barbiturates : Clinical uses

- Induction :
  - Thiopental 3-4 mg/kg IV bolus
  - Increase dose in Pediatrics : 5-6 mg/kg
- Barbiturate coma :
  - Pentobarbital 10 mg/kg IV in 30 mins then 5 mg/kg/hour for 3 hrs

Barbiturates : Side effects

- Hypotension
- Apnea , inadequate ventilation
- Laryngospasm , bronchospasm
- Venoirritation (pH 10.6)
- Accidental intraarterial injection → intense vasoconstriction → gangrene
  - Treatment : dilution of drug by saline injection, heparinization to prevent thrombosis, sympathetic blockade (BPB)

Barbiturates : Side effects

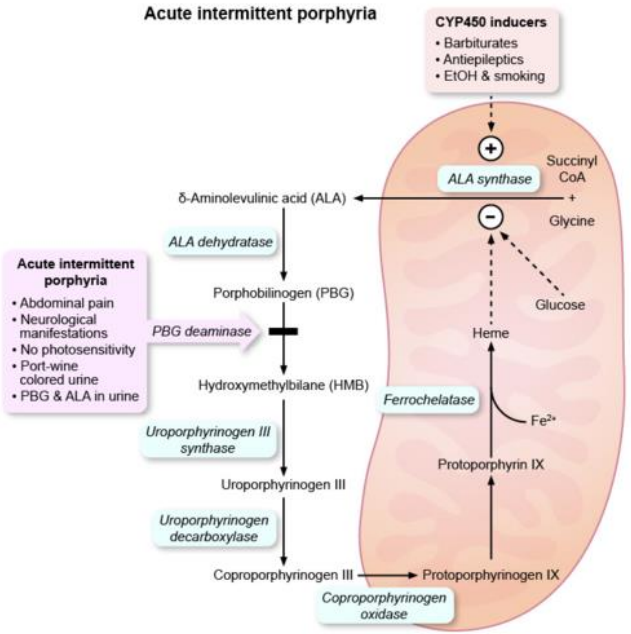
- Allergic reaction (facial edema, hives, bronchospasm, anaphylaxis) : rare
- Transient urticarial rash
- Garlic or onion taste

Barbiturates : Contraindication

- Acute intermittent porphyria and variegate porphyria
- Shock, Severe hypovolemia or CV instability
- Respiratory obstruction
- Asthma
- Allergy

Barbiturates : Contraindication

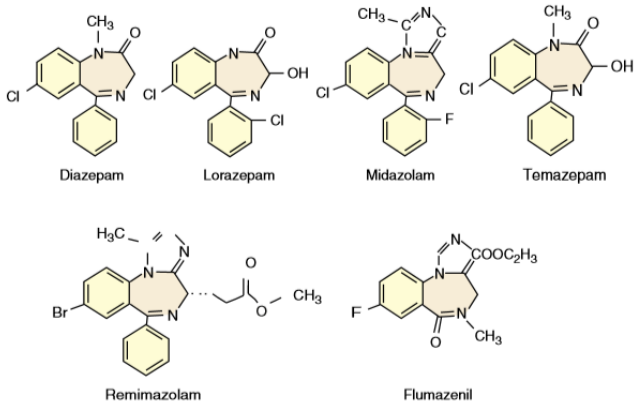
- Porphyria attack (Severe abdominal pain, nausea, vomiting, psychiatric disorders, and neurologic abnormalities)
    - Acute intermittent and variegate porphyria
    - Due to induction of δ-aminolevulinic acid synthetase which catalyzes the rate limiting step in the biosynthesis of Porphyrins



3. Benzodiazepine

Benzodiazepine : Chemical Structure

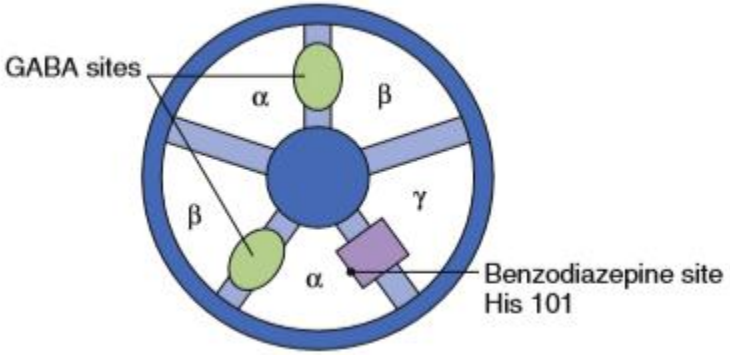
- Diazepam
  - Water insoluble
  - Precipitated with NSS, Sterile water
- Lorazepam
  - Water insoluble
- Midazolam
  - Water soluble in vitro (acidic medium)
  - Lipid soluble in vivo



Benzodiazepine : Mechanism

- Bind to benzodiazepine receptor in GABA receptor → Enhance response to GABA by facilitating the opening of Cl channel → Hyperpolarization

- Receptor affinity (Potency) :
  - Lorazepam > Midazolam > Diazepam



Benzodiazepine : Pharmacokinetic

- Midazolam
  - Oral : Bioavailability < 50%, Onset 30-80 mins
  - IV : rapid onset, distribution hL 7-15 min
  - Metabolite : oxidation by CYP3A4, CYP3A5 (low hepatic extraction ratio 0.3-0.44) -> 1-OH midazolam (active metabolite)
  - Conjugated with glucuronide -> excreted by kidney
  - Factors effect PK : Obese, Age, Hepatic cirrhosis, Renal impairment

Benzodiazepine : Pharmacokinetic

- Diazepam
  - Oral : Bioavailability = 94%, Peak plasma concentration 60 minutes
  - Metabolite : Oxidation and Conjugation by CYP2C1, CYP3A4 → N-desmethyldiazepam (active metabolite, elimination t1/2 200 hrs → prolonged sedation)
  - Factors effect PK : Obese, Liver function, Age

Benzodiazepine : Pharmacokinetic

- Lorazepam
  - Oral : Bioavailability 90%, Peak plasma concentration 2 hrs.
  - Metabolite : Conjugate to glucuronic acid → Inactive metabolites
  - Factors effect PK : clearance is decreased by hepatic dysfunction

Benzodiazepine : Pharmacokinetic

- Remimazolam
  - Short-acting GABAA receptor agonist.
  - Metabolite : Nonspecific esterase in plasma → carboxylic acid metabolites (CNS 7054)
  - More rapid onset, greater depth of sedation and more rapid recovery > Midazolam
  - Level and duration of sedation are dose dependent

Benzodiazepine : Pharmacodynamic (CNS)

- Hypnotic, Sedative, Anxiolytic, Amnesic, Anti-convulsant and centrally produced muscle relaxant
- Cerebral metabolism (CMRO2) ↓, cerebral blood flow ↓(metabolic coupling) → Normal ratio of CBF/CMRO2, ICP ↓
- Neuroprotective effects (Prevent lipid peroxidation and mitochondrial damage)

Benzodiazepine : Pharmacodynamic (CVS)

- Modest hemodynamic effects
- Dose-dependent : SVR ↓ → BP ↓ ; CO, HR ↔
- Preserve homeostatic reflex mechanism

Benzodiazepine : Pharmacodynamic (RS)

- Dose dependent Central RS depression
  - Muscle tone ↓ → Risk of Upper airway obstruction ↑
  - Flatten respiratory curve to carbon dioxide
  - Depress hypoxic ventilatory response
  - TV ↓, MV ↓

Benzodiazepine : Clinical uses

- Induction, Maintenance of anesthesia, Sedation

TABLE 23.7 Uses and Doses of Intravenous Benzodiazepines

	Midazolam	Diazepam	Lorazepam
Induction	0.05-0.15 mg/kg	0.3-0.5 mg/kg	0.1 mg/kg
Maintenance	0.05 mg/kg prn	0.1 mg/kg prn	0.02 mg/kg prn
	1 μg/kg/min		
Sedation*	0.5-1 mg repeated	2 mg repeated	0.25 mg repeated
	0.07 mg/kg IM		

Benzodiazepine : Clinical uses

- Premedication
  - Anxiolysis, sedative, anterograde amnesia, reduction of PONV
  - Diazepam : 5-10 mg PO, 1-2 hrs. before anesthesia
  - Lorazepam : 2-4 mg PO, 2 hrs. before anesthesia
  - Midazolam : 7.5-15 mg PO, 30-60 mins before anesthesia
- Nausea and Vomiting prophylaxis
  - Midazolam 0.075 mg/kg IV after induction (middle ear surgery, laparoscopic gynecologic surgery)

Benzodiazepine : Side effects

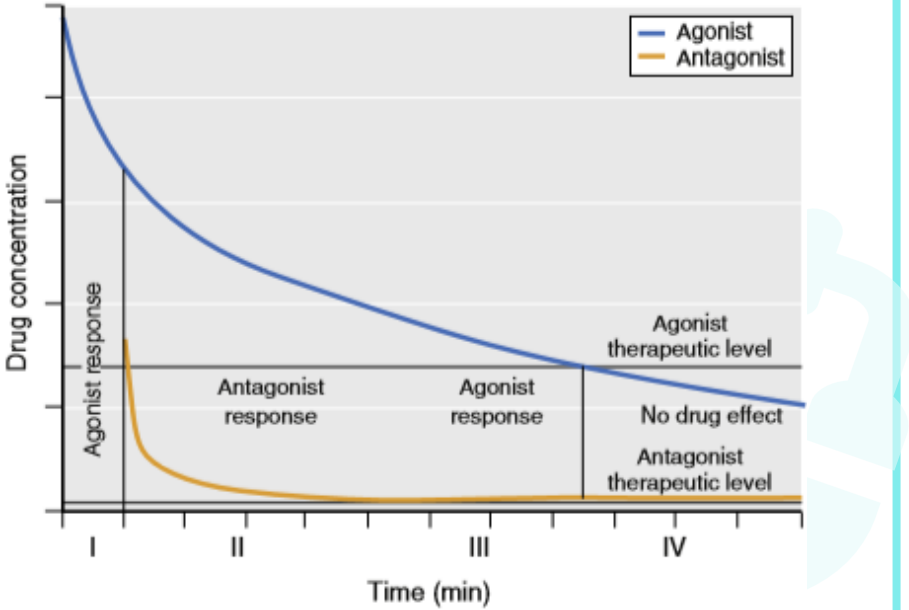
- RS depression
- Venous irritation
- Thrombophlebitis

Flumazenil

- Competitive antagonist at BZD receptor
- Reverse sedative, RS depression, amnesia effect of BZD
- Minimal intrinsic activity
- Rapid metabolite at liver (Elimination t1/2 = 1 hr. → Risk of resedation)

Flumazenil

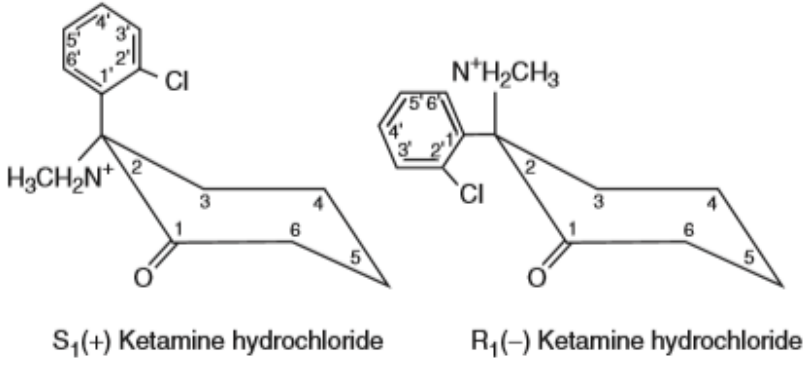
- Reversal of benzodiazepines
  - 0.2 mg repeated up to 3.0 mg
- Diagnosis of coma
  - 0.5 mg repeated up to 1.0 mg
- An infusion rate of 30 to 60 mcg/min (0.5-1 mcg/kg/min)



4. Ketamine

Ketamine : Chemical Structure

- Partially water-soluble compound, lipid solubility = 5-10 times of Thiopental
- Two optical isomers = S(+) , R(-)
  - S(+)isomer is 3 times more potent as analgesic with faster clearance and recovery
- Protein binding 12%



$S_1(+)$ Ketamine hydrochloride

$R_1(-)$ Ketamine hydrochloride

Ketamine : Mechanism

- Multiple receptors include :
  - GABAergic system
  - NMDA receptor antagonist
  - Opioid receptors
  - Muscarinic receptors
  - Monoaminergic receptors

Ketamine : Mechanism

- “Functional Disorganization”
  - Selective depress neuronal function of Cortex and Thalamus
  - Stimulating Limbic systems including hippocampus

Ketamine : Pharmacokinetic

- Highly lipid soluble -> Rapid onset = 30-60 sec
- Distribution t1/2 11-16 min, elimination t1/2 2-3 hrs
- Oral bioavailability 20-30%, Nasal bioavailability 40-50%
- Metabolite : Cytochrome p-450 (N-demethylation) → Norketamine (20-30% active)
- Conjugated with glucuronide → excreted by kidney
- High hepatic extraction ratio

Ketamine : Pharmacodynamic (CNS)

- Dose-dependent CNS depression
- Dissociative anesthesia : “Cataleptic state” ; profound analgesia and amnesia BUT open eyes and maintain many reflexes (corneal, cough, swallow)
- Cerebral metabolism (CMRO2) ↑, cerebral blood flow ↑, ICP ↑ (excitatory CNS effects)

Ketamine : Pharmacodynamic (CNS)

- Analgesic effect occurs at low blood concentration by inhibit NMDA receptor
- Nystagmus, dilatation of pupils
- Lacrimation and salivation
- ↑ Skeletal muscle tone

Ketamine : Pharmacodynamic (CVS)

- Cardiovascular stimulations : sympathetic stimulation, catecholamine release, inhibit NE reuptake, Inhibit vagal nerve (Caution in prolonged septic shock, Trauma)
- HR ↑, BP ↑, CO ↑, Myocardial oxygen consumption
- Intrinsic myocardial depression
- PAP ↑, contraindicated in poor right ventricular reserve

Ketamine : Pharmacodynamic (RS)

- Minimal respiratory depression
- Bronchodilators
- Increased salivation

Ketamine : Clinical uses

- Induction
  - Dose : 0.5-2 mg/kg IV
  - Onset = 30-60 sec, peak effects = 1 mins
  - Duration = 10-15 min, full orientation to person, place, time in 15-30 min
- Sedation and analgesia
  - Dose : 0.2-0.8 mg/kg IV in 2-3 min

Ketamine : Clinical uses

- Preemptive or preventive analgesia
  - Dose : 0.15-0.25 mg/kg IV
  - Acute pain : Opioid sparing effect (decrease SE e.g. PONV)
  - Chronic pain : cancer pain, chronic peripheral and central neuropathic pain , phantom limb pain, etc.

Ketamine : Side effects

- Emergence reaction : Vivid dreaming, extracorporeal experiences, illusion (Depression of auditory and visual relay nucleli)
    - ↑ by dose, age, female, psychological susceptibility and concurrent drugs
    - ↓ by benzodiazepines, barbiturates or propofol
- Post-operative delirium
- Liver and renal toxicity in abuse, chronic pain

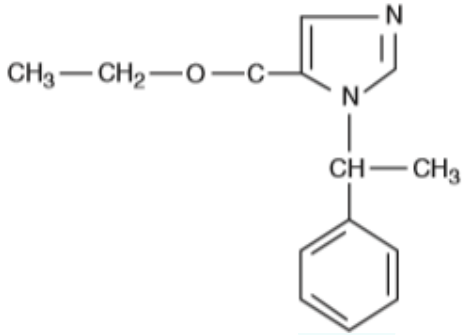
Ketamine : Contraindication

- Increased intracranial pressure
- Open eye injury
- Coronary artery disease
- Vascular aneurysms
- Psychiatric disorders

5. Etomidate

Etomidate : Chemical Structure

- Imidazole group
- pKa 4.2, hydrophobic at physiologic pH
- 0.2% solution in 35% propylene glycol (Amidate) or lipid emulsion (Etomidate-Lipuro)



Etomidate : Mechanism

- Low dose : Positive modulation of GABA receptor → Lower GABA require to activate GABA receptor
- Supraclinical concentration : Directly activate GABA receptor

Etomidate : Pharmacokinetic

- Three compartment model
- Metabolite : Ester hydrolysis at Liver to inactive metabolite
- Hepatic extraction ratio 0.5
- Excrete : Kidney (85%), Bile (15%)
- Protein binding 75%

Etomidate : Pharmacodynamic (CNS)

- Cerebral metabolism (CMRO2) ↓, cerebral blood flow ↓, ICP ↓
- MAP ↔, CPP ↔
- Etomidate can induce convulsion-like EEG potentials in epileptic patients
- IOP ↓

Etomidate : Pharmacodynamic (CVS)

- Hemodynamic stability
- No effect of sympathetic nervous system or baroreceptor

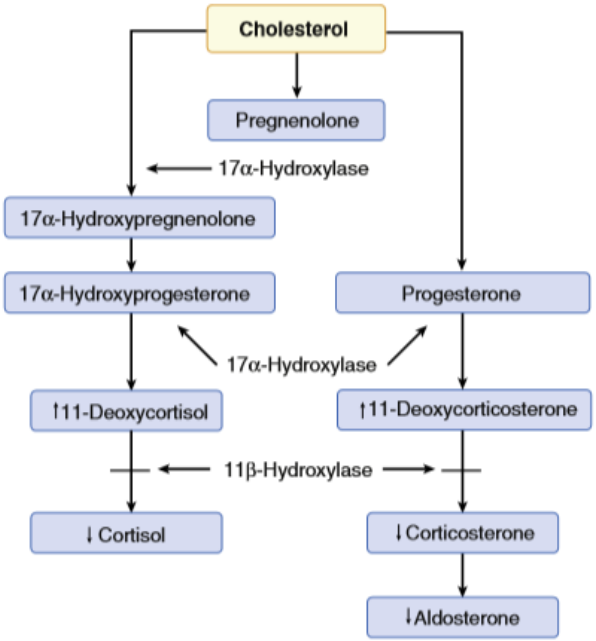
Etomidate : Pharmacodynamic (RS)

- Less effect on ventilation
- Not induce histamine release

Etomidate : Pharmacodynamic (Endocrine)

- Adrenal cortical suppression
- Inhibit enzyme 11-β-hydroxylase → Cortisol ↓, Aldosterone ↓
- The impact of single dose etomidate in critically ill patients remains unclear

Etomidate : Pharmacodynamic (Endocrine)



Etomidate : Clinical uses

- Induction
  - Dose = 0.2-0.6 mg/kg IV
  - One arm-brain circulation → Rapid onset
  - Suitable in CVS disease, Reactive airway disease, ICP ↑
- Treatment of Hypercortisolemia

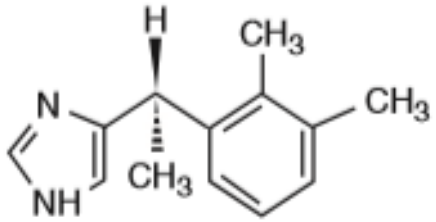
Etomidate : Side effects

- PONV
- Myoclonus
- Pain on injection
- Hiccup

6. Dexmedetomidine

Dexmedetomidine : Chemical Structure

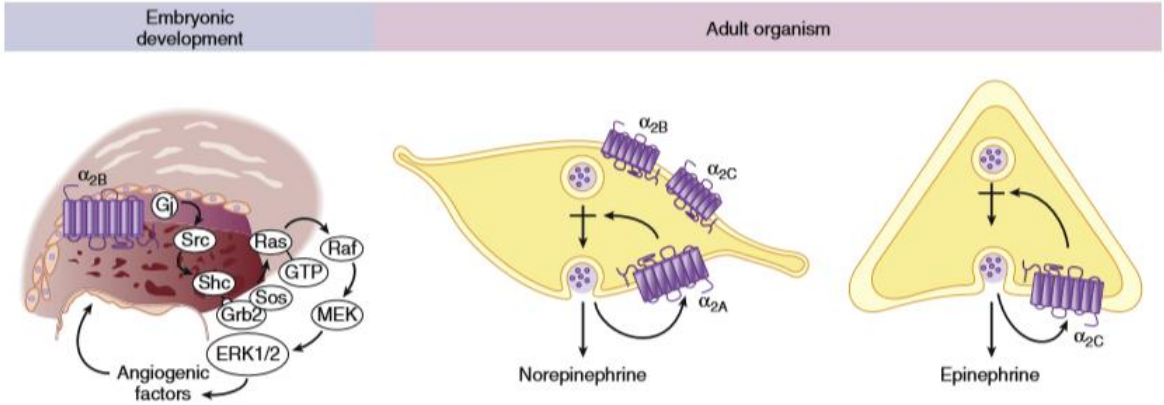
- Imidazole group
- α2-adrenergic receptor agonists
- α2/α1 = 1600:1 (clonidine 220:1)
- Dilute with 5%DW, NSS, RLS



Dexmedetomidine : Mechanism

- Sedative :
    - Effect on α2 in locus caeruleus → Decrease projection to Ventrolateral preoptic nuclei
- Analgesia :
    - Effect on α2 in dorsal horn → suppressing pain transmission pathway

Dexmedetomidine : Mechanism



Physiologic functions of α_2-adrenergic receptor subtypes

α_{2B}	α_{2A}	α_{2C}
• Hypertension • Placental angiogenesis • Hypertensive effect of etomidate • Analgesic effect of nitrous oxide	• Presynaptic feedback inhibition of norepinephrine release • Hypotension • Analgesia • Sedation • Inhibition of epileptic seizures	• Feedback inhibition of adrenal catecholamine release • Analgesic effect of moxonidine • Modulation of behavior

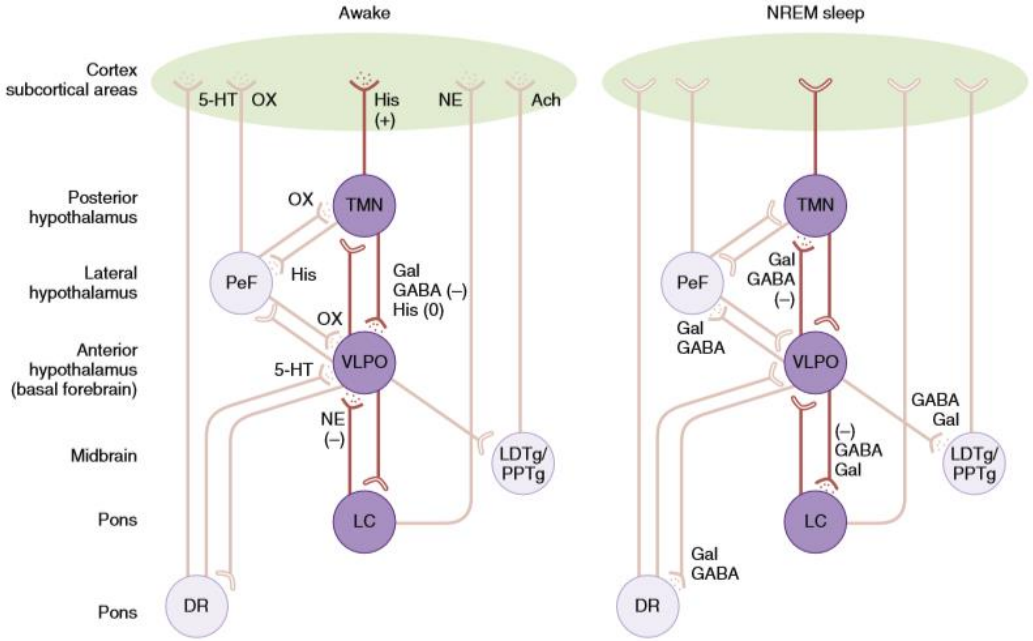
Dexmedetomidine : Pharmacokinetic

- Protein binding 94%
- Metabolite : glucuronidation, hydroxylation (CYP2A6) and N-demethylation at Liver to inactive metabolite
- Excrete : Kidney, Feces
- Can be reversed by Atipamezole

Dexmedetomidine : Pharmacodynamic (CNS)

- Sedative, anxiolytic, analgesic, hypnotic effects
- Cerebral metabolism (CMRO2) ↓, cerebral blood flow ↓
- Preserve CO2 responsiveness, autoregulation
- Generate natural sleep patterns → Easy to wake up and have ability to follow command and cooperate

Dexmedetomidine : Pharmacodynamic (CNS)



Dexmedetomidine : Pharmacodynamic (CVS)

- Transient hypertension (postsynaptic α-2 adrenoreceptors in peripheral blood vessels)
- Hypotension (presynaptic α-2 adrenoreceptors inhibit NE release) HR ↓, CO ↓

Dexmedetomidine : Pharmacodynamic (RS)

- MV ↓
- Normal PaO_2, pH and slope of CO_2 ventilatory response curve

Dexmedetomidine : Clinical uses

- Intraoperative uses :
  - Premedication dose : 0.33-0.67 mcg/kg IV before surgery
  - Sedation : cooperative with sparing respiratory function → awake fiberoptic intubation, awake craniotomy, awake carotid endarterectomies, regional anesthesia
  - Opioid sparing effect during anesthesia : craniotomy, bariatric surgery, → improve perioperative hemodynamic stability, ↓ RS depression

Dexmedetomidine : Clinical uses

- ICU use :
  - Sedation : 0.5-1 mcg/kg IV then 0.1-1 mcg/kg/hr
  - Hemodynamic stable
  - Minimal RS depression → Good PaO2/FiO2 ratio
  - Opioid sparing effects
  - Decrease risk of delirium or coma during sedation
  - FDA approve for infusion < 24 hours

Dexmedetomidine : Side effects

- Dry mouth (decrease salivation)

Thank you