INTRAVENOUS ANESTHETICS AGENTS

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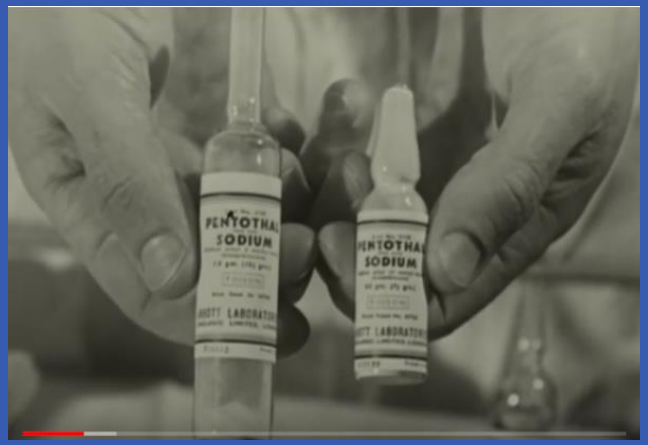
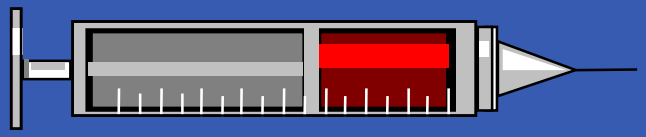

SODIUM
SODIUM

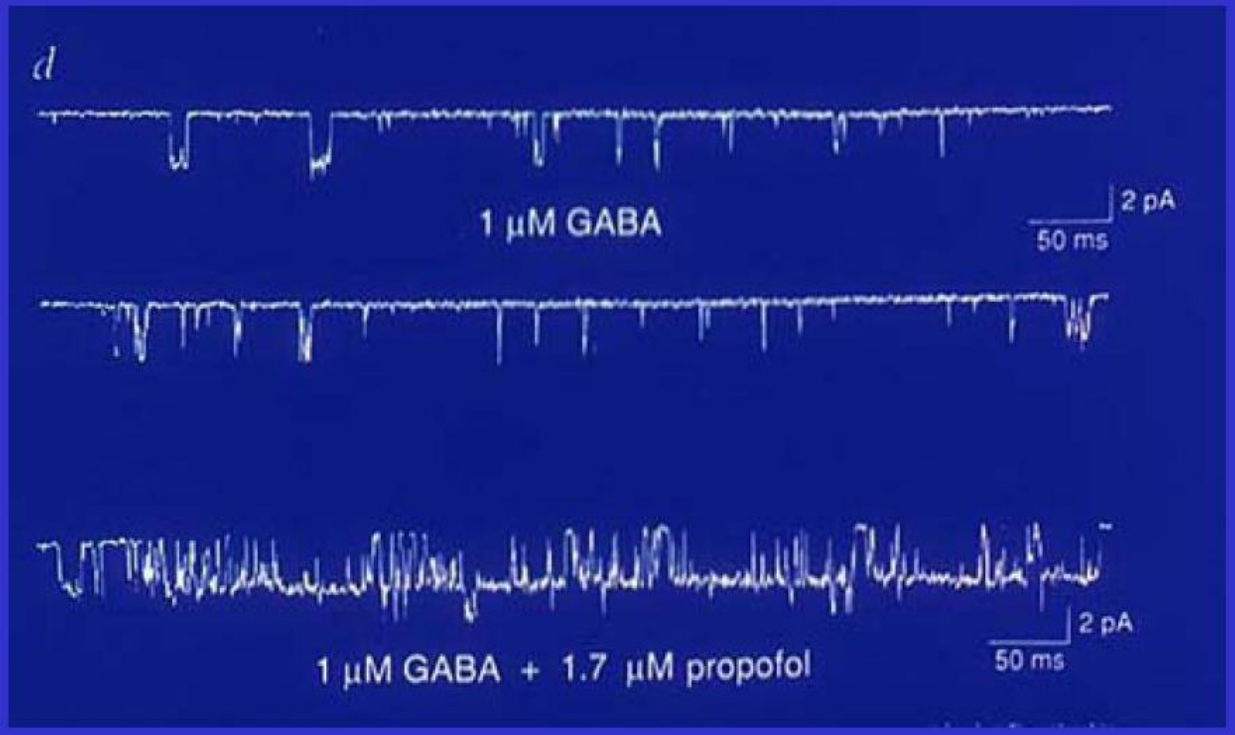
Goals of General Anesthesia

- Hypnosis (unconsciousness)
- Amnesia
- Analgesia
- Immobility/decreased muscle tone
  - (relaxation of skeletal muscle)
- Reduction of certain autonomic reflexes
  - (gag reflex, tachycardia, vasoconstriction)

Intravenous Anesthetics



Anesthetics prolong ion channel opening of GABA receptors



Anesthetic drugs

- A drug that induces reversible anesthesia
- The state of loss of sensations, or awareness.

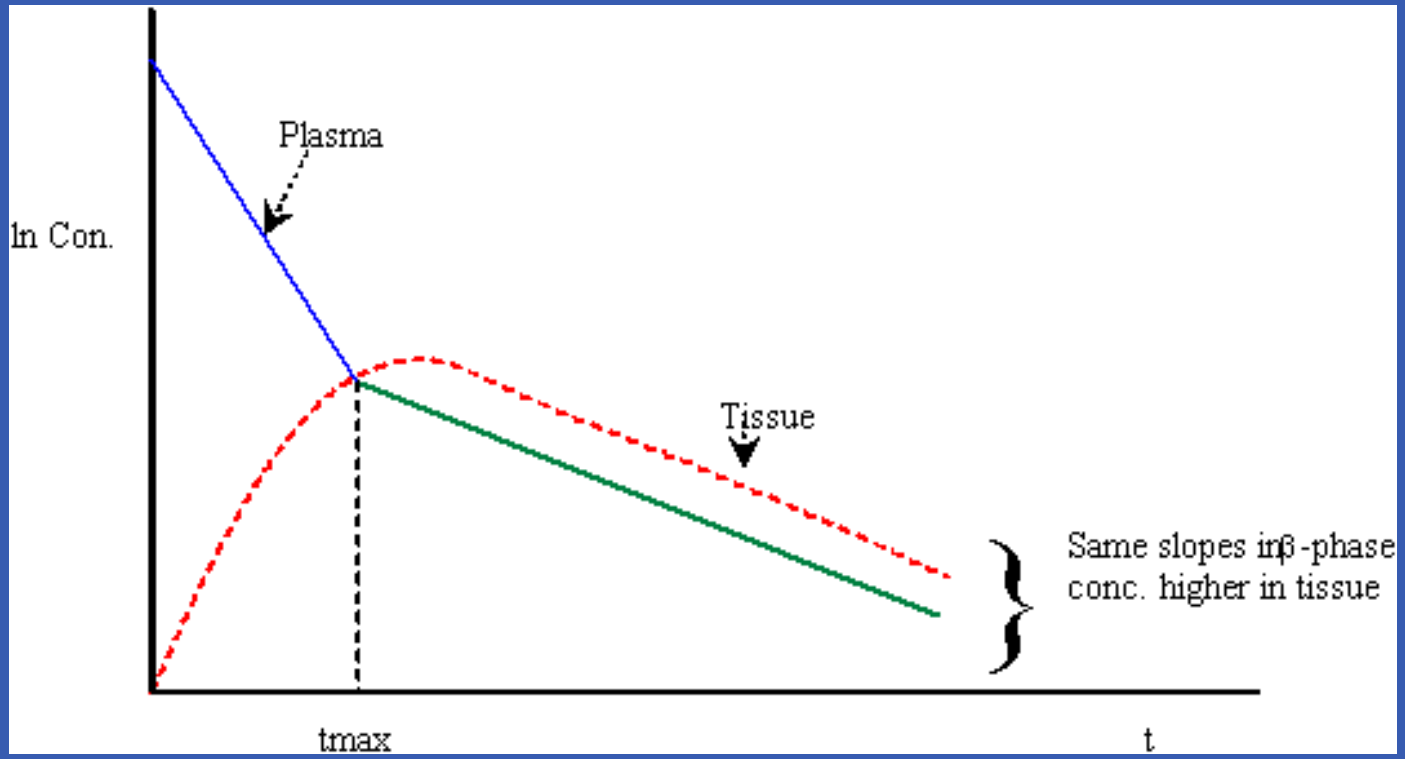
- Either stimulates an inhibitory neuron, or inhibits an excitatory neuron.

Pharmacological Principles

- Organs are divided according to blood perfusion:
- High- perfusion organs (vessel-rich); brain takes up disproportionately large amount of drug compared to less perfused areas (muscles, fat, and vessel-poor groups).
- After IV injection, vessel-rich group takes most of the available drug
- Drugs bound to plasma proteins are unavailable for uptake by an organ
- After highly perfused organs are saturated during initial distribution, the greater mass of the less perfused organs continue to take up drug from the bloodstream.
- As plasma concentration falls, some drug leaves the highly perfused organs to maintain equilibrium.

- This redistribution from the vessel-rich group is responsible for termination of effect of many anesthetic drugs.

- **Compartment Model**



Protein sites of action

- **Inhibitory channels :**
  - GABA-A channels (the main inhibitory receptor).
  - Glycine channels.

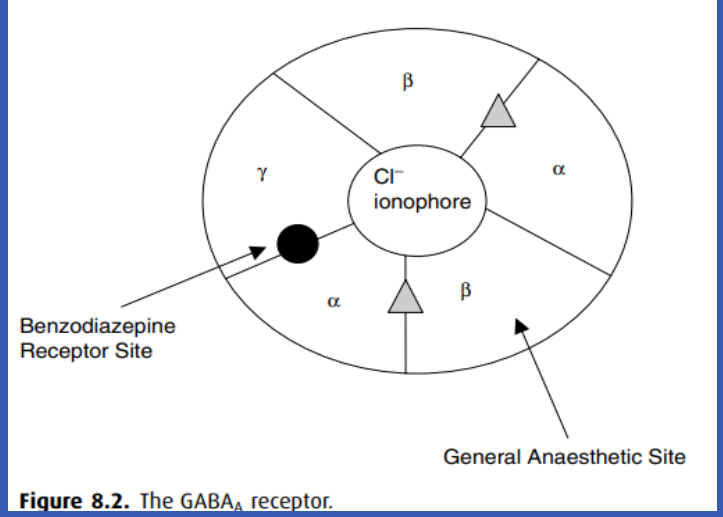
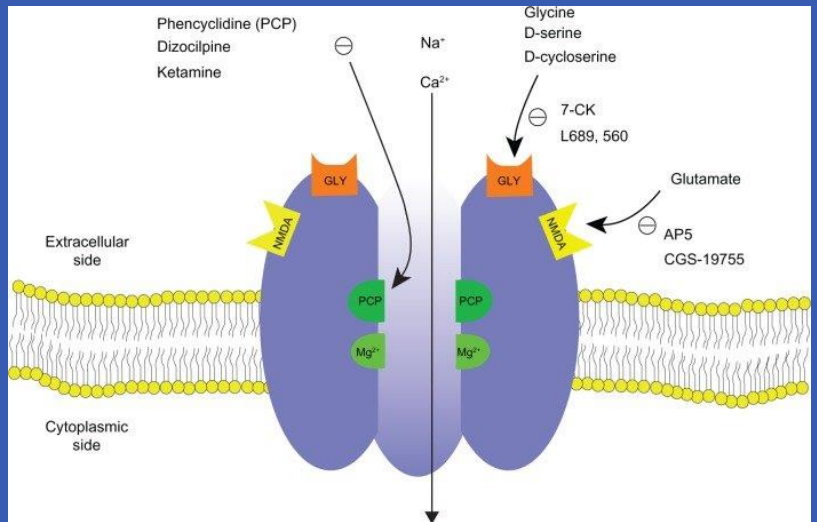


Figure 8.2. The $GABA_A$ receptor.

- **Excitatory channels :**
  - Neuronal nicotic.
  - NMDA.



The ideal intravenous anaesthetic agent

- Rapid onset (mainly unionized at physiological pH)
- High lipid solubility
- Rapid recovery, no accumulation during prolonged infusion
- Analgesic at sub- anaesthetic concentrations
- Minimal cardiovascular and respiratory depression
- No emetic effects
- No pain on injection
- No excitation or emergence phenomena
- No interaction with other agents
- Safe following inadvertent intra-arterial injection
- No toxic effects
- No histamine release /No hypersensitivity reactions
- Water-soluble formulation
- Long shelf-life at room temperature

INTRAVENOUS ANAESTHETIC

- **Barbiturate**
  - ✓ Sodium thiopental(used for over 40 years)
  - ✓ Methohexital
- **Non barbiturate**
  - ✓ Propofol
  - ✓ Ketamine (infrequently used)
  - ✓ Etomidate
  - ✓ benzodiazepines
- **Other** adjuvant intravenous anesthetic agents (opioid / Dexmedetomidine)

BARBITURATES

- After the clinical introduction of thiopental by Waters and Lundy in 1934, thiopental became preferred clinically because of its rapid onset of action and short duration, without the excitatory effects of hexobarbital (first)

- Depress the RAS located in the brain stem that controls several vital functions & consciousness

- MOA :
  (1) enhancement of the synaptic actions of inhibitory neurotransmitters on the $GABA_A$ receptor altering the **duration** Cl- channel spend in an open state
  (2) blockade of the synaptic actions of excitatory neurotransmitters NMDARs

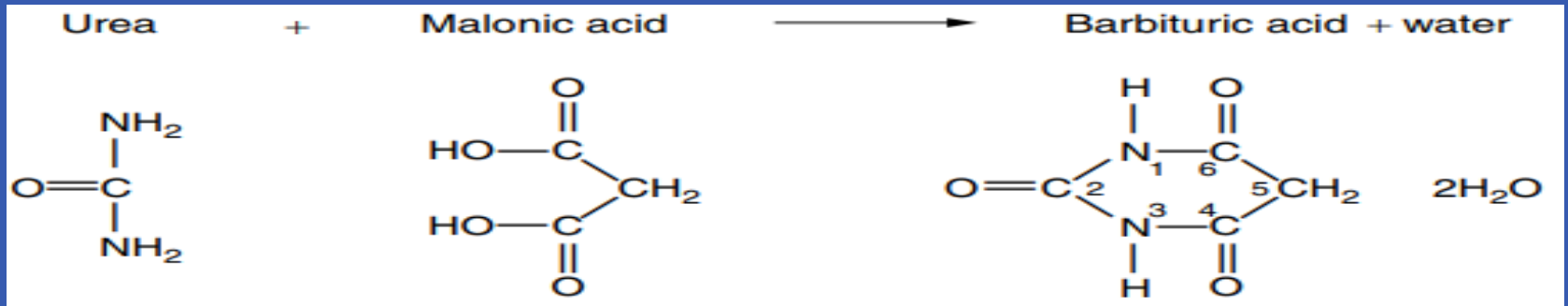
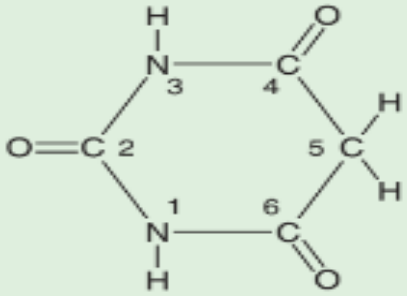
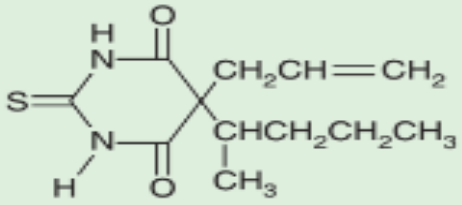


Figure 8.3. Formation of barbituric acid.

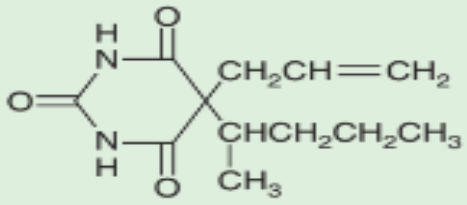
Barbituric acid



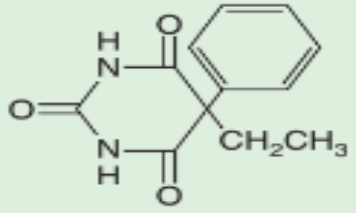
Thiamylal



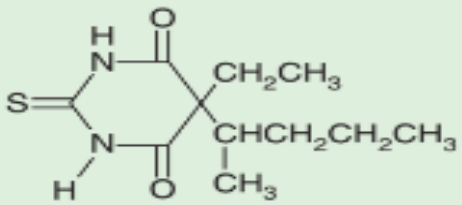
Secobarbital



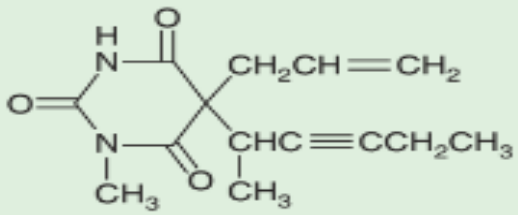
Phenobarbital



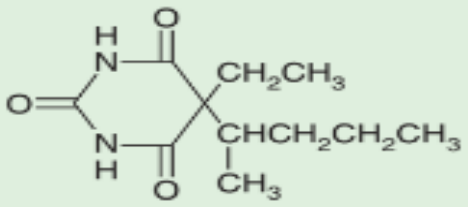
Thiopental



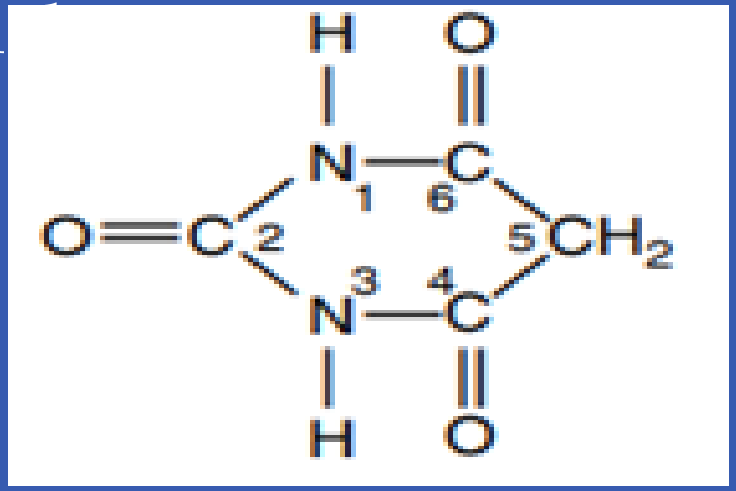
Methohexital



Pentobarbital



- The two major classes of barbiturates are the oxybarbiturates and thiobarbiturates (oxygen or sulfar at c2)
- In general, thiobarbiturates are very lipid soluble, highly protein bound and completely metabolized in the liver. (more rapid onset of action, as with thiopental)
- In contrast, the oxybarbiturates are less lipid-soluble, less protein bound, and some are excreted almost entirely unchanged in



- the substitution of the hydrogen attached to the carbon atom in position 5 with aryl or alkyl groups gives the barbiturates their hypnotic and sedative effects.

- Barbiturates are not readily soluble in water at neutral pH. Their solubility depends on transformation from the keto to the enol form (tautomerism) ,which occurs most readily in alkaline solutions

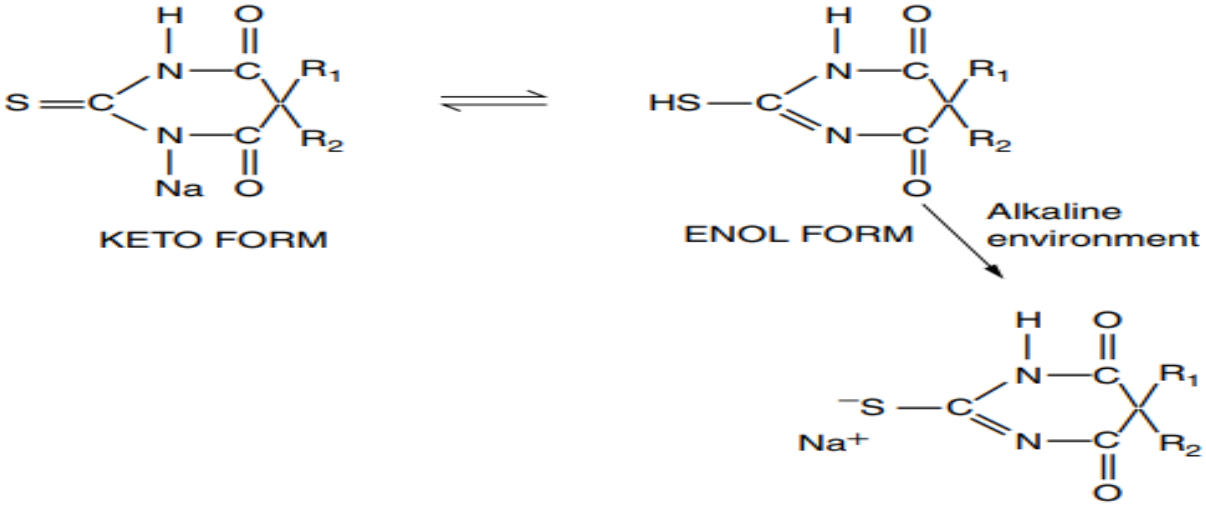


Figure 8.4. Keto-enol transformation of barbiturates – tautomerism. Alkaline solutions favour the water-soluble enol form.

PHARMACOKINETICS

- The barbiturates (with the exception of phenobarbital >> renal excretion accounts for 60% to 90% in an unchanged form) are metabolized hepatically. The metabolites are almost all inactive, water soluble, and excreted in the urine.
- barbiturates are excreted unchanged by the kidney only in trivial amounts.

- The hepatic enzyme induction by barbiturates is the reason that they are not recommended for administration to patients with acute intermittent porphyria.
- Barbiturates may precipitate an attack by stimulating δ-aminolevulinic acid synthetase, the enzyme responsible for the production of porphyrins

SODIUM THIOPENTAL (PENTOTHAL)

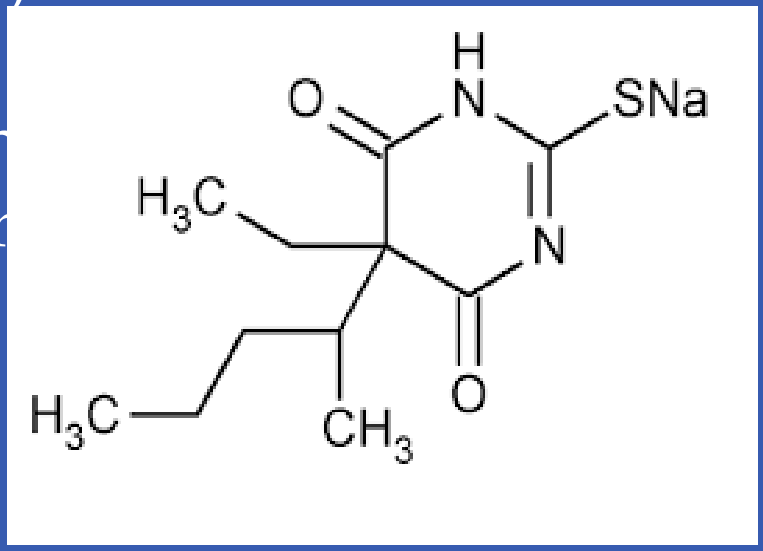
- It's a Yellow powder with a sulphuric smell and a bitter taste
- Highly lipid soluble compound
- combined with sodium carbonate >> water soluble enol form > desirable as a preparation. (PH 10.5)
- Injected > neutralized > lipid soluble non ionized form(40% ionized at ph=7.4)
- Dosing: 3-5 mg/kg >>

30-60 secs after administration

>> "arm brain" circulation tim

- anesthetic state persists for

5-10 mins (Ultra short)



Pharmacokinetics

- protein binding by albumin(75%)
  - Sulphur containing drug.. Acidosis (ill pt), NSAIDS may displace thiopental from albumin
  - Liver & renal disease may be associated with low albumin levels so result in an increase in free thiop… toxicity
- It is bacteriostatic in water and has a ph of 10.6 to10.8
- **short duration of action** > due to its **redistribution** away from central circulation towards muscle and fat tissue
- Metabolism: primarily in the liver with approximately 10 to 15% of the drug level metabolized per hour.
- Less than 1% of the drug is excreted unchanged in the urine.

Effects

- **Cardiovascular :**
  - dose-dependent reduction in CO, SV and BP that may provoke a compensatory tachycardia.
  - Coronary blood flow, HR & myocardial O2 uptake all increase
  - little change in total peripheral resistance
  - effects are profound in hypovolemic, acidotic and have reduced protein binding patient.
- **Respiratory :**
  - respiratory depression is dose-dependent.
  - FRC is reduced by 20% with induction of anesthesia
  - 2 or 3 large breaths followed by apnea for less than 1min
  - It may produce a degree of laryngospasm and bronchospasm. (light level of anesthesia)

- **Central nervous system :**
  - There is a reduction in cerebral oxygen consumption, blood flow, blood volume and cerebrospinal fluid pressure.
  - it can be used **to stop seizures activity in emergency situations.**
  - To maintain depression of cerebral electrical activity very high dose are required but to maintain seizure control & avoid cardiovascular depression from high dose of thiopental other drugs are used (e.g. benzodiazepines)
  - **Elevated ICP** can quickly be reduced by thiopental BUT The improvement of ICP requires high dose of thiopental to be maintained
  - **Intraocular pressure decreases** up to 25% with 3-5mg/kg of thiopental and persists for 3 to 5 minutes.
  - When used in very low doses it is antanalgesic. (decrease pain threshold.)

- **GI:**
  - Enzyme induction (with prolonged high dose therapy).
  - Hypoalbuminemia > increase in the potency of thiopental.

- **Renal:**
  - urine output may fall >> due to increased ADH release secondary to central nervous system depression, and reduced cardiac output

- **Severe anaphylactic reactions**:
  - seen in approximately 1 in 20 000 administrations of thiopental.

- **Porphyria** : >> absolutely contraindicated in patients with porphyria. Also other barbiturates / Etomidate / Enflurane etc ..

- although thiopental crosses the placenta it has NO significant effect on the fetus when used for c/sections (dose used is limited to 4mg/kg).

uses

- Induction of anesthesia
- Maintenance of anesthesia for short procedures.
- Control of convulsive states
- To supplement regional anesthesia.

Side effect

- Hypotension esp. in hypovolemic, shocked ones.
- Respiratory depression: in excessive doses
- Tissue necrosis.
- Laryngeal spasm.
- Bronchospasm: unusual but in asthmatics pts.
- Allergic reactions: from coetaneous rashes to severe anaphylactic shock with CVS collapse.

- Rarely, Intra-Arterial injection can occur. And precipitation of thiopental crystals which become wedged into small blood vessels leading to ischemia and pain
- Degree of injury is related to the concentration of the drug.

Treatment consists of :

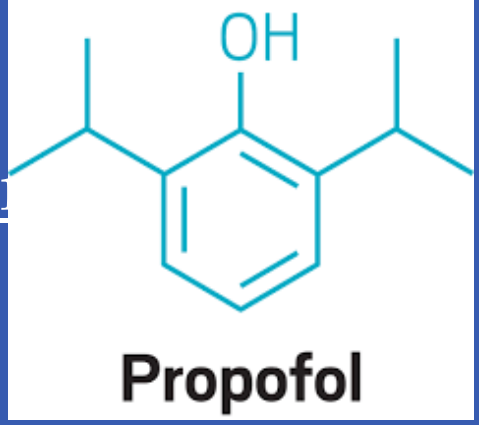
1. Dilution of the drug by the administration of saline into the artery.
2. Heparinization to prevent thrombosis.
3. Intra-arterial injection of papaverine or procainea and analgesia.
3. Brachial plexus block, stellate ganglion block, vasodilators

- Overall, the proper administration of thiopental intravenously is remarkably free of local toxicity

PROPOFOL 1970s

- (IV) induction drug of choice for most patients.
- The initial solution of propofol was released in 1977 in Cremophor EL. It was withdrawn because of anaphylactic reactions and was replaced and reformulated as an emulsion of a soybean oil–propofol mixture in water and relaunched in 1986.
- Propofol is used for induction and maintenance of anesthesia and for sedation in and outside the operating room
- MOA : activation of ($GABA_A$) receptor complex,. (increase binding affinity of GABA to the receptor) + antagonist of the (NMDA) receptor

- Propofol is one of a group of alkylphe
(highly lipid soluble) that were explored
for their hypnotic properties in animals.



- The formulation most commonly used is that of
  - 1% propofol
  - 10% soybean oil
  - 1.2% purified egg phospholipid added as emulsifier
  - 2.25% of glycerol as a tonicity-adjusting agent
  - sodium hydroxide to change the pH.
  - regarding microbial growth in the emulsion, ethylenediaminetetraacetic acid (EDTA) was added for its bacteriostatic activities.

- Propofol has a pH of 7 and appears as a slightly viscous, milky white substance, a result of small lipid droplets in solution.
- In Europe, a 2% formulation and contains a mixture of MCT and LCT .{medium chain ,and long chain Triglycerides}
- All formulations commercially available are stable at room temperature, are not light sensitive, and may be diluted with 5% dextrose in water
- It is a weak organic acid with a pKa = 11 so that it is almost entirely unionized at pH 7.4

- **Dosing :** 1 to 2.5 mg/kg (plasma concentration of 4–8 µg/ml) reducing the initial dose and titrating propafol in increments IN older age / Hypovolemia or myocardial dysfunction / Coadministration of one or more adjuvant

PHARMACOKINETICS

- 98% protein bound to albumin
- Largest volume of distribution of all the induction agents at 3-12 l/kg.
- highly lipid-soluble, resulting in very rapid onset. 1.5 to 2.6 minutes (arm brain circulation).

- Following bolus administration, its duration of action is short due to the rapid decrease in plasma levels as it is distributed to well-perfused tissues , redistribution and elimination (two-compartment and three-compartment models).

- The initial distribution half life of propofol is 2 to 8 minutes.
- The context sensitive half-time for propofol for infusions of up to 8 hours is less than 40 minutes

- Propofol is oxidized and conjugated in the liver. metabolites >> inactive.
- excreted by the kidneys.
- Less than 1% propofol is excreted unchanged in urine, and only 2% is excreted in feces.

- The clearance of propofol is extremely high, 1.5 to 2.2 L/minute>> 20 to 30 mL/kg/minute) exceeds hepatic blood flow >> extrahepatic metabolism or extrarenal elimination.
- Renal metabolism accounts for up to 30% of propofol clearance, (lungs also 20 to 30%)

- propofol has a high extraction ratio, this may impair its own clearance by decreasing cardiac output and thus hepatic blood flow (contrast in hemorrhagic compensated shock)

- In term and preterm neonates, variability of propofol clearance (maturation of clearance) >> Dosage must be calculated with extreme care.
- Children have a relatively larger central compartment volume (50%) and a more rapid clearance (25%) >> weight adjusted
- Women have a larger volume of distribution and higher clearance rates, but the elimination half-life is similar for male and female patients.
- Older individuals have decreased clearance rates and a smaller central compartment volume. (decrease dose 50%)

- Hepatic disease > larger central compartment volumes + clearance is unchanged, but the elimination half-life is slightly prolonged, as is time to recovery. (no significant dose adjustment extrahepatic)

- Competitive inhibition of cytochrome P450 system activity >> competition of two drugs (e.g., propofol and midazolam)

Effects

- **Cardiovascular**:
  - the SVR falls resulting in a drop in BP.
    reflex tachycardia is rare and propofol is usually associated with a bradycardia especially with opioids.
    Sympathetic activity and myocardial contractility are also reduced.

- **Respiratory :**
  - respiratory depression leading to apnoea is common. It is rare to observe cough or laryngospasm following its use and so it is often used in anaesthesia for ease of placement of a laryngeal mask.

- **Central nervous system :**
  - excitatory effects in up to 10% of patients. not represent true cortical seizure activity; rather they are subcortical excitatory–inhibitory centre imbalance. The movements are dystonic with choreiform elements and opisthotonos.
    - Propofol has been used to control status epilepticus

- **Gut :**
  - some evidence exists to suggest that propofol possesses anti-emetic properties following its use for induction, maintenance or in subhypnotic doses postoperatively.
  - Anatagonism of the dopamine D2 receptor is a possible mechanism.

- **Pain :**
  - injection into small veins is painful but may be reduced using lidocaine or if a larger vein is used.

- **Metabolic :**
  - a fat overload syndrome, with hyperlipidaemia, and fatty infiltration of heart, liver, kidneys and lungs can follow prolonged infusions especially in children.

- **Miscellaneous** :
  - it may turn urine and hair green.
    It's anti-pruretic

Advantages

- rapid onset (30 to 45 seconds) and recovery
- Antiemetic properties.
- Antipruritic properties. (for patients who will receive opioids, which often cause pruritus) .
- Bronchodilatory properties with decreased airway resistance (bronchospasm and asthma)
- Anticonvulsant properties (decreases ($CMRO_2$), with consequent reduction in (CBF) and (ICP).
- Suitability for patients with renal and/or hepatic insufficiency

Adverse effects

- Dose-dependent hypotension + (HR) is minimally affected / systolic (BP) decreases to <90 mmHg in 16 percent of patients / take care in hypovolemic or hemodynamically compromised, as well as in older patients .

- Dose-dependent respiratory depression

- Pain on injection. two-thirds of patients due to venous irritation caused by propafol itself rather than its lipid emulsion .
  - Typically, lidocaine and/or an opioid is coadministered with propofol to minimize this pain . (eliminated or reduced in hemodynamicly instable patient).
  - Injection of propofol into a larger or central vein also minimizes pain.

- Contamination risk. Despite of antimicrobials, propafol preparations support rapid bacterial growth due to the lipid emulsion containing egg lecithin, glycerol, and soybean oil. Fever, infection, sepsis, and death have been reported . Risk is minimized by:
  1. Using an aseptic technique in drug preparation
  2. Avoiding multidose use from a single vial for more than one patient
  3. Discarding opened propafol after six hours

- Rare allergic reactions .
  - Patients allergic to eggs are usually allergic to egg protein or albumin. The egg component of the propofol preparation is lecethin, which is a phosphatide, therefore it is unlikely that allergic reactions are due to these components of its preparation.

  - Propofol does not appear to be allergenic in patients who are sensitive to soya beans because all protein within the soya bean oil is removed.

- not appear to cause any adverse effects when given intra-arterially, although onset of anaesthesia is delayed.

Propofol infusion syndrome

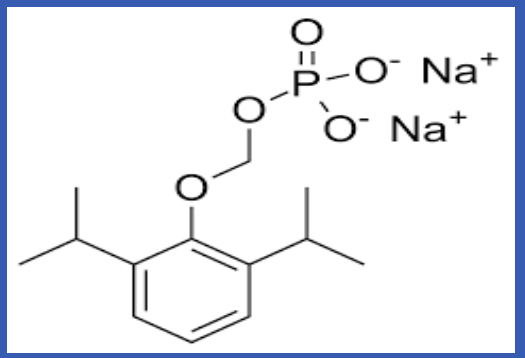
- is a rare but lethal syndrome
- infusion of propofol at 4 mg/kg/ hour or more for 48 hours or longer. (for only 3 hours one case)
- first described in children but subsequently in critically ill adults.
- The clinical features are acute refractory bradycardia leading to asystole in the presence of one or more of the following:
  - ✓ metabolic acidosis (base deficit >10 mmol/L)
  - ✓ rhabdomyolysis,
  - ✓ Hyperlipidemia
  - ✓ enlarged or fatty liver.
- Other features include cardiomyopathy with acute cardiac failure, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia.

- The symptoms and signs are the result of muscle injury and the release of intracellular toxic contents.

- The major risk factors are poor oxygen delivery, sepsis, serious cerebral injury, and large propofol dosage.
- Predisposing factors are likely:
  - genetic disorders impairing fatty acid metabolism, such as medium-chain acyl coenzyme A (MCAD) deficiency and low carbohydrate supply.
  - a failure of hepatic lipid regulation, possibly related to poor oxygenation or a lack of glucose, may be the cause.

- In some cases, increasing lipemia was the first indication of impending propofol infusion syndrome onset; therefore, lipemia is a sign

Fospropofol



- In 2008, the U.S.(FDA) approved fospropofol disodium (Lusedra), for monitored anesthesia care in adult patients undergoing diagnostic and therapeutic procedures. (more complete amnesia and better conscious sedation)
- water-soluble prodrug of propofol
- Fospropofol protein binding is extensive (98%)
- Fospropofol is metabolized by alkaline phosphatases in the liver to active metabolite propofol, formaldehyde, and phosphate.
- Formaldehyde is further metabolized to formate, which is then eliminated, primarily by oxidation to carbon dioxide
- One millimole of propofol is generated for each millimole of fospropofol sodium administered

- This drug has a small volume of distribution of 0.3 L/kg (slower onset) and a total body clearance of 0.36 L/kg/hour with a terminal elimination half-life of 0.88 hours (slower recovery)

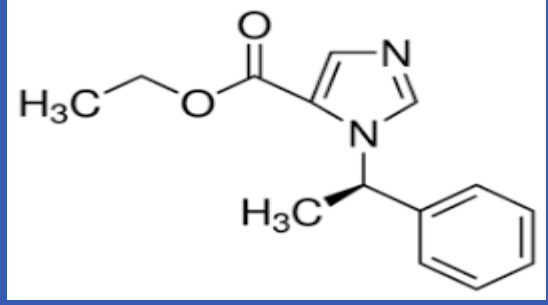
- The pharmacokinetics of fospropofol and liberated propofol is not affected by race, sex, mild to moderate renal impairment , age or alkaline phosphatase concentration.

- So far, no pharmacokinetic interactions have been found between fospropofol and fentanyl, midazolam, morphine, or propofol. fospropofol is not subject to cytochrome P450 enzyme-mediated metabolism

- not associated with pain on injection

- mild to moderate perineal paresthesias and pruritus minutes after a bolus injection of fospropofol >> phosphate metabolite

ETOMIDATE



- an imidazole derivative that acts direct on ($GABA_A$) receptor complex (increase affinity), blocking neuroexcitation and producing anesthesia /amnesia/ no analgesia.
- rapid onset without changes in (BP),(CO), or (HR) >> (most hemodynamically neutral) >> commonly used in the emergency setting as part of a rapid sequence induction or for conscious sedation
- Dosing : 0.15 to 0.3 mg/kg iv / typical dose being 20 mg/ reduced in Coadministration of other adjuvant + Severe hypotension or shock
- repeated bolus doses of etomidate should **NOT** be administered so that further inhibition of cortisol biosynthesis is avoided

Pharmacokinetics

- very rapid onset of action , similar to propofol.
- arm brain circulation is 1.6 minutes.
- short duration of action (3 to 12 minutes) because it is rapidly redistributed from the brain to other tissues.
- The volume of distribution is 2.5 to 4.5 L/kg.
- Clearance of etomidate is high (18 - 25 mL/kg/minute). Terminal elimination half-life is three to five hours.
- The main route of metabolism is ester hydrolysis in the liver and plasma, and the metabolites are inactive.
- Etomidate is highly protein bound in blood plasma.

Advantages

- Superior hemodynamic stability compared with other induction agents. Etomidatee does not cause vasodilation or myocardial depression, and does not increase sympathetic tone. Thus, BP and HR remain stable.

- most favorable therapeutic index (ratio of median lethal dose [LD_{50}] to median effective dose [EC_{50}]).

- Rapid onset and recovery, similar to propofol.

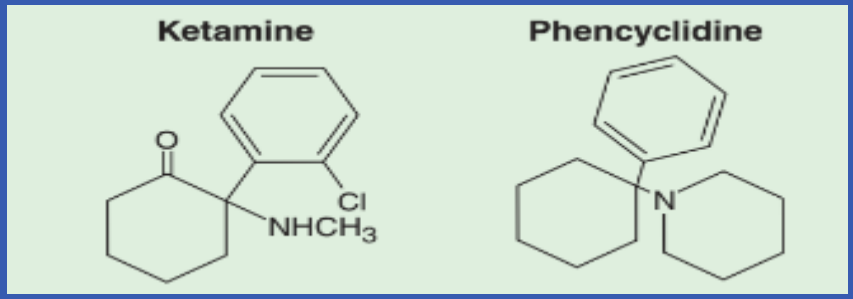
- Anticonvulsant properties. Etomidatee decreases ($CMRO_2$),(CBF) and (ICP). Thus, it may be advantageous in hemodynamically unstable patients with head injury or stroke.

Adverse effects

- A high incidence 30% of (PONV) compared with propofol.
- Pain on injection 80% of patients >> venous irritation /low pH (6.9) of the 35% propylene glycol used in formulations. >> injecte into a larger or central vein Or coadminister of lidocaine or an opioid (avoided in hemodynamic instability).
- Dose-related involuntary myoclonic movements in 50 to 80 % of patients . due to subcortical disinhibition and is unrelated to cortical seizure activity >> Coadministration of an opioid or benzodiazepine typically attenuates myoclonus (avoided in hemodynamic instability pt).
- Absence of any analgesic effect. not blunt the sympathetic stress response to noxious stimulation of the upper airway during laryngoscopy and intubation. (in patients with cardiovascular disease or elevated ICP, prior administration of an opioid and/or lidocaine may attenuate the stress response)
- Mild increase in airway resistance.

- Transient acute adrenal insufficiency. It transiently inhibits cortisol biosynthesis (reversible inhibition of 11-beta-hydroxylase (which converts 11-deoxycortisol to cortisol) / lasting <24 hours), this is not harmful in most clinical settings and does not preclude its use. To avoid further suppression of cortisol, we do not administer multiple bolus doses or infusions of etomidate.
- use of etomidate in patients with frank septic shock may increase the likelihood of development of adrenal insufficiency
- If etomidate has been used in a septic patient who subsequently develops refractory hypotension, a stress dose of a glucocorticoid should be administered (eg, [IV] hydrocortisone 100 mg or dexa 4 mg).
- However, we do NOT administer prophylactic glucocorticoids in other settings.

Ketamine



- 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 (profound analgesia while appearing disconnected from surroundings)
- noncompetitive antagonism of glutamate (NMDA) receptor antagonist
- Also, ketamine excites opioid receptors within the insular cortex, putamen, and thalamus, thereby producing analgesia.
- Structurally analogue to phencyclidine
- Can cause hallucinogenic effects and nightmares

- Ketamine is the only induction agent that stimulates catecholamine receptors (increasing sympathetic tone) , producing increases in BP, HR, contractility, (PAP), and (CBF) .
- Also, ketamine reduces vasodilation by decreasing the production of vascular nitric oxide
- Ketamine may be selected to induce anesthesia in hypotensive patients or those likely to develop hypotension during induction due to hypovolemia, hemorrhage, sepsis, or severe cardiovascular compromise.

- Dosing : 1 to 2 mg/kg IV . The IM induction dose is 4 to 6 mg/kg.
- coadministered with other adjuvant have additive or infra-additive (antagonistic) rather than synergistic effects.
- lower initial dose :
  - ✓ Chronic use of a tricyclic antidepressant, since both drugs inhibit norepinephrine reuptake
  - ✓ Severe hypotension or shock in a patient whose catecholamine reserves may be depleted

Pharmacokinetics

- very rapid speed of onset / arm brain circulation of <1 minute. (15 to 30 minute in IM) variable absorption from muscle tissue.
- The primary metabolite (by liver) of ketamine is norketamine(one-tenth to one-third of ketamine's potency) . Norketamine contributes to total time until return of consciousness after an induction dose (9 to 20 minutes) as well as the analgesic effects, which last longer than the anesthetic effects .
- More lipid soluble and less protein bound than thiopental
- The Vd 3 L/kg . Clearance is similar to liver blood flow (15 to 20 mL/kg/minute).
- Neither renal nor moderate hepatic dysfunction has a clinically significant effect on ketamine clearance. The terminal elimination half-life is two to three hours
- Excreted renally

Effect

Cardiovascular:

- Increases BP, HR, CO , PAP and myocardial work
- Avoid in coronary artery disease or hypertensive patient (pheo).
- Intrinsic mild myocardial depressant properties that are normally overcome by increased sympathetic tone, but may become apparent in the critically ill patient with depleted catecholamine reserves (eg, profound hypovolemic, septic, or cardiogenic shock)

  . Since these depressant effects are dose-related, induction doses are reduced in a patient with profound hypotension (mean arterial pressure [MAP] <50 mmHg) or shock

Respiratory:

- Minimal effect on the ventilatory drive
- Potent bronchodilator
- increases salivation and upper airway secretions, this side effect is not relevant during induction of general anesthesia

Cerebral

- Possible increased cerebral metabolism with increased sympathetic stimulation.(not significantly).
- Sympathomimetic effects that increase CBF and (ICP) in spontaneously breathing patients.
- Unique EEG effects that may result in misinterpretation of processed EEG values (eg, [BIS])

- Myoclonic activity is associated increased subcortical electrical activity
- Undesirable psychotomimetic effects (illusions, disturbing, nightmares,vivid dreams and delirium) >> Prior administration of a benzodiazepine may minimize these effects
- Have analgesic effects
- Possible neurotoxicity. Animal studies

Advantages

- Increases sympathetic tone with consequent increases in BP, HR, and CO in most patients . However, these increases do not occur if presynaptic catecholamine stores are depleted.
- Bronchodilatory properties. Ketamine is useful in patients with bronchospasm and/or asthma.
- Maintains airway reflexes and respiratory drive. Useful maintening spontaneous respiration .
- Profound analgesic properties, even in sub-hypnotic doses. Intraoperative administration of ketamine reduces postoperative opioid consumption in patients with chronic pain, opioid tolerance, or hyperalgesia
- Rapid onset and recovery after (IV) , similar to propofol .
- Alternative routes of administration, in a severely agitated uncooperative patient with no iv access, (IM) injection is feasible. For children, oral or rectal administration is also possible.

Drug-drug interactions

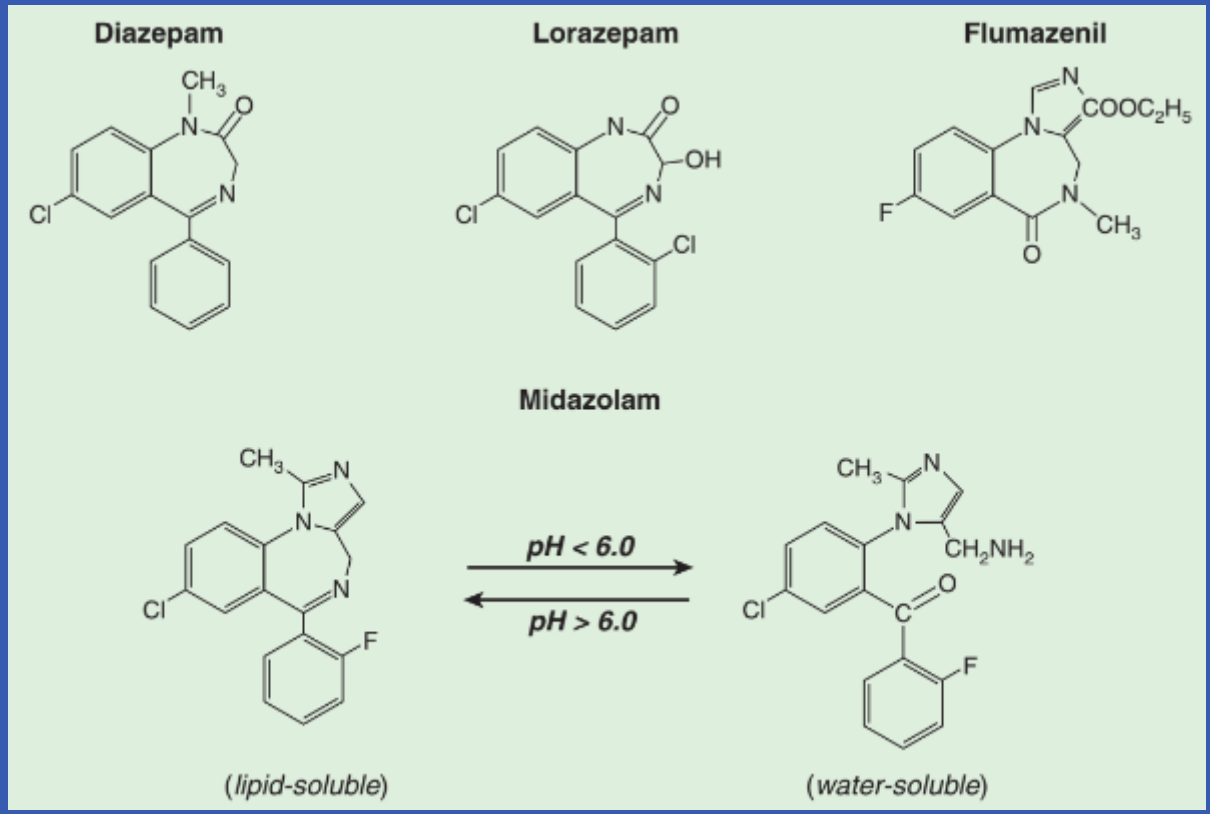
- Ketamine is avoided if cocaine use is suspected. Cocaine's cardiovascular toxicity may be potentiated by the sympathomimetic effects of ketamine and lead to myocardial ischemia, arrhythmias, and pulmonary hypertension.
- In patients taking a tricyclic antidepressant, a low initial induction dose of ketamine is administered (eg, 1 mg/kg) because both agents inhibit norepinephrine reuptake.
- Coadministration of a volatile anesthetic agent during induction may result in synergistic anesthetic effects. The induction dose is reduced in this circumstance

Benzodiazepines

- Interact with specific receptors in the CNS mainly in the cortex
- Binding to receptors (different site) enhances the inhibitory effects of various neurotransmitters (GABA)

  (increases the frequency of openings)
- Flumazenil is a specific benzodiazepine-receptor antagonist that effectively reverses most of the CNS effect
- Chemical structure includes a benzene ring and a 7-member diazepine ring, substitution ay various positions on these rings affect potency and biotransformation

Agent	Use	Route	Dose
Diazepam	Premedication	Oral	0.2-0.5 mg/kg upto 15 mg
	Sedation	IV	0.04-0.2 mg/kg
	Induction of hypnosis	IV	0.3-0.6 mg/kg
Midazolam	Premeditation	IM	0.07-0.15 mg/kg
	Sedation	IV	0.01-0.1 mg/kg
	Induction of hypnosis	IV	0.1-0.4 mg/kg
Lorazepam (not Recommended in children)	Premedication	Oral	0.05 mg/kg
		IM	0.03-0.05 mg/kg
	Sedation	IV	0.03-0.04 mg/kg


Diazepam
Lorazepam
Flumazenil
Midazolam
pH < 6.0
pH > 6.0
(lipid-soluble)
(water-soluble)

Pharmacokinetics

- 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 (insoluble in water so parenteral preparations contain propylene glycol, which can produce venous irritation)..
- Diazepam is lipid soluble and rapidly cross the blood brain barrier, water soluble at low pH
- Redistribution is rapid for benzodiazepines (3-10 min)
- Highly protein bound (90-98%)
- Rely on the liver for transformation into water-soluble glucoronide end products
- Slow hepatic extraction, long half-life for diazepam (30h)
- Metabolites are excreted mainly in the urine
- Entrohepatic circulation produces a second peak in diazepam plasma concentration 6-12h following administration

Effect

Cardiovascular

- Minimal CVS depressant effects
- Arterial BP, Cardiac output, and PVR slightly decreased
- Heart rate sometimes increased

Respiratory

- Depresses ventilatory response to CO_2
- Ventilation must be monitored

Cerebral

- Reduces cerebral oxygen consumption
- Decreases cerebral blood flow and intracranial pressure
- Effective in preventing and controlling grand mal seizures
- Sedative dosages cause antegrade amnesia

Dexmedetomidine

- Is a sedative medication used by intensive care units and anesthesiologists, brand name Precedex
- unique > sedation without causing respiratory depression
- MOA: agonism of alpha-2 receptors in certain parts of the brain
- It is the S-enantiomer of medetomidine
- Has sedative, analgesic, sympatholytic, and anxiolytic effects
- Reduces the volatile anesthetic, sedative and analgesic requirements of the patient without significant respiratory depression
- Effective tx for the dangerous cv symptoms of cocaine intoxication and overdose
- Has an opiod sparing effect
- dosage is 1 µg/kg IV over 10 min / infusion rate of 0.2-0.7 µg/kg/hr
- Metabolized in the liver and metabolites eliminated in the urine
- Side effects include bradycardia, heart block and hypotension

Opioids narcotic analgesics

- Name derived from Poppy juice (opium), first obtained from the capsules of the unripe oriental Poppy seed (papaver somniferum), of which Morphine is the principal active ingredient.
- "Opiates": a term generally used for naturally occurring substances with properties similar to Morphine.
- "Opioids" : refers to all naturally occurring and synthetic drugs with an affinity for opioid receptors, and actions that can be stereospecifically antagonized by Naloxone
- MOA: interaction with Specific opioid receptors in the CNS (brain and Spinal Cord) and peripheral tissues (somatic and sympathetic nerves) /Modifying the complex emotional experience of pain and affecting its transmission as a sensory modality.

Opioid Receptors

- ✓ **μ (mu): with μ-1 and μ-2 subtypes**
- ✓ **Κ (kapa)**
- ✓ **δ (delta)**
- ✓ **σ (sigma)**

- The pharmacodynamic properties of specific opioids depend on which receptor is bound, the binding affinity, and whether the receptor is activated.

- Opioid receptors can also be activated by some endogenous peptides (Endorphins, enkephalins, and dynorphins)

- Opioid receptor activation inhibits the presynaptic release and post-synaptic response to excitatory neurotransmitters (e.g. Acetyl-choline, substance P).

Receptor	Clinical effect	Agonist examples
μ (mu)	- Supra-spinal analgesia (μ-1) - Respiratory Depression (μ-2) - Physical dependence - Muscle rigidity	Morphine Met-enkephalin Beta endorphin Fentanyl
κ (kapa)	- Sedation - Spinal analgesia	Morphine Nalbuphene Butorphanol Dynorphins Oxycodone
δ (delta)	- Analgesia - Behavioral - Epileptogenic	Leu-Enkephalin Beta endorphin
σ (sigma)	- Dysphoria - Hallucinations - Respiratory stimulation	Pentazocine Nalorphine Ketamine?

Opioids classification

- **Agonists**: linear Dose-Response relationship / Stimulate **μ** and **κ** receptors / Antagonized by Naloxone and Nalorphine
  - ✓ ***Strong***: Morphine, pethidine, Methadone, Fentanyl
  - ✓ ***Moderate:*** Codeine, Oxycodone, Hydrocodone
  - ✓ ***Weak***: Propoxyphene

- **Mixed agonist/antagonist:** plateau or bell shaped Dose response curve / Antagonists at **μ** receptor above low dose / Full or partial agonists at **κ** receptor / Antagonized by Naloxone but not by Nalorphine
  - ✓ Pentazocine, butorphanol, nalbuphene, Buprenorphine, Nalorphine

- **Antagonists**:
  - ✓ Naloxone has a higher affinity for **μ** receptor than for other opioid receptors.
  - ✓ Doxapram is used to treat the respiratory depression caused by Buprenorphine since its effects are only partially reversed by Naloxone.
  - ✓ Naloxone, Naltrexone, Doxapram

Pharmacokinetics

- Distribution half lives of all opioids are fairly rapid: 5-20 minutes.
- Re-distribution is responsible for termination of action of small doses
- Morphine has low fat solubility accounting for its slow onset and prolonged duration of action.
- Most opioids depend on the liver for biotransformation, with high hepatic extraction ratio.
- Morphine has both active and inactive metabolites
- Pethidine (Meperidine) is metabolized to the active noremeperidine.
- Remifentanyl has a unique ester structure ➔ rapid ester hydrolysis: terminal elimination half life of 10 minutes.

- Excretion of end products of opioids metabolism is mainly through the kidney
- Noremeperidine has an excitatory effect on CNS leading to Myoclonic activity and seizures that are not reversed by Naloxone
- A late secondary peak in Fentanyl plasma level may occur 4 hours after last IV dose due to enterohepatic recirculation and release of sequestered drug.
- Morphine-3-glucuronide is partly excreted in bile and can be broken down by intestinal bacteria, releasing morphine that may be reabsorbed by Enterohepatic recirculation.

effect

- **Cardiovascular :**

Meperidine	↑H/R, ↓cardiac contractility, Histamine release in some individuals
Morphine	↓H/R at high doses (vagus mediated), histamine release
Fentanyl, sufentanyl, Remifentanyl alfentanyl	↓H/R at high doses
Combination with other anesthetics	? Significant myocardial depression

- Depress ventilation, particularly RR. Hypoxic drive is decreased.
- ↑Resting PaCO2 with blunted ventilatory response to CO2 challenge.
- Apneic threshold is elevated.
- Histamine release - bronchospasm: (Morphine and Meperidine).
- Chest wall rigidity: Fentanyl, sufentanyl, alfentanyl.
- blunt the airway reflexes to airway management

Cerebral

- In normal brains, Opioids reduce cerebral Oxygen Consumption, CBF, and ICP, but to a much lower degree than barbiturates or benzodiazepines.
- Meperidine:? EEG activation.
- Stimulation of CRTZ➔ Nausea & Vomiting.
- not reliably produce amnesia.
- effectively used in intra- thecal and epidural spaces for analgesia.
- Meperidine: has local anesthetic qualities and effectively used to treat shivering.

Gastro-intestinal

- Contraction of sphincter of Oddi and biliary spasm .
- Constipation

Genitourinary: Urine retention

Endocrine:

- More effective than inhalational anesthetics in blocking the stress response to surgical stimulation.

Ophthalmic: Miosis

Summary of Intravenous Anesthetic Agents

Drug	Speed of Induction and Recovery	Main Unwanted Effects	Notes
Thiopental	Fast (accumulation occurs, giving slow recovery) Hangover	Cardiovascular and respiratory depression	Used as induction agent declining. Decreases cerebral blood flow and O2 consumption.
Etomidate	Fast onset, fairly fast recovery	Excitatory effects during induction and recovery, Adrenocortical suppression	Less cardiovascular and respiratory depression than with thiopental, Causes pain at injection site
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.
Ketamine	Slow onset, after-effects common during recovery	Psychotomimetic effects following recovery, Postoperative nausea, vomiting and salivation	Produces good analgesia and amnesia
Midazolam	Slower than other agents		Little respiratory or cardiovascular depression

Table 8–8. Summary of nonvolatile anesthetic effects on organ systems.

	Cardiovascular		Respiratory		Cerebral		
Agent	HR	MAP	Vent	B'dil	CBF	$CMRO_2$	ICP
Barbiturates							
Thiopental	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Thiamylal	↑↑	↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓↓
Methohexital	↑↑	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Benzodiazepines							
Diazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Lorazepam	0/↑	↓	↓↓	0	↓↓	↓↓	↓↓
Midazolam	↑	↓↓	↓↓	0	↓↓	↓↓	↓↓
Opioids							
Meperidine*	↑	*	↓↓↓	*	↓	↓	↓
Morphine*	↓	*	↓↓↓	*	↓	↓	↓
Fentanyl	↓↓	↓	↓↓↓	0	↓	↓	↓
Sufentanil	↓↓	↓	↓↓↓	0	↓	↓	↓
Alfentanil	↓↓	↓↓	↓↓↓	0	↓	↓	↓
Remifentanil	↓↓	↓↓	↓↓↓	0	↓	↓	↓
Ketamine	↑↑	↑↑	↓	↑↑↑	↑↑↑	↑	↑↑↑
Etomidate	0	↓	↓	0	↓↓↓	↓↓↓	↓↓↓
Propofol	0	↓↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓
Droperidol	↑	↓↓	0	0	↓	0	↓

*The effects of meperidine and morphine on MAP and bronchodilation depend upon the extent of histamine release.

HR = heart rate; MAP = mean arterial pressure; Vent = ventilatory drive; B'dil = bronchodilation; CBF = cerebral blood flow; $CMRO_2$ = cerebral oxygen consumption; ICP = intracranial pressure.

0 = no effect.

0/↑ = no change or mild increase.

↓ = decrease (mild, moderate, marked).

↑ = increase (mild, moderate, marked).

Sources :

- ✓ Up To Date
- ✓ Miller's anesthesia 8th edition
- ✓ Pharmacology of anesthesia and intensive care


The end