Intravenous Anesthetic Agents

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Intravenous Anaesthesia :

Properties of Intravenous Anesthesia :

- Developed **later** than **inhalational** anaesthesia.
- used commonly to induce anaesthesia
- induction is usually **smoother** and more **rapid** than most of the inhalational agents.
- preferred now because it is **faster** with **less** risk of **excitement** or laryngospasm
- may also be used for maintenance, either alone or in combination with nitrous oxide

Intravenous Anaesthesia :

Properties of Intravenous Anesthesia :

- they may be administered as repeated bolus doses or by continuous i.v. infusion.
- Used for sedation during regional anaesthesia
- used for sedation in the intensive care unit (ICU)
- used for treatment of status epilepticus.
- Used as the sole drug for short procedures (deep sedation)

Properties of The Ideal Intravenous Anaesthetic Agent:

Physical properties:

- Water soluble & stable in solution
- Stable on exposure to light
- Long shelf life
- No pain on intravenous injection
- Painful when injected into an artery
- Non-irritant when injected subcutaneously
- Low incidence of thrombophlebitis
- Cheap

Properties of The Ideal Intravenous Anaesthetic Agent:

Pharmacokinetic properties :

- Rapid onset in one arm-brain circulation time
- Rapid redistribution to vessel rich tissue
- Rapid clearance and metabolism
- No active metabolites

Properties of The Ideal Intravenous Anaesthetic Agent:

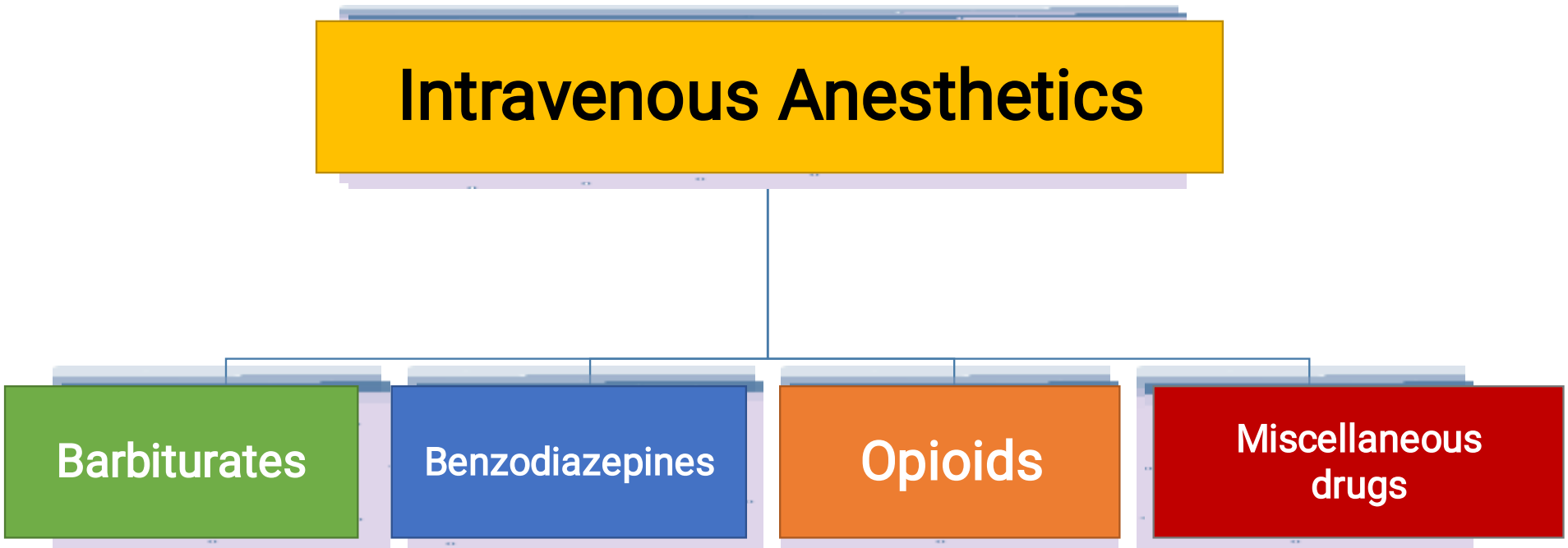
Pharmacodynamics properties :

- High therapeutic ratio (ratio of toxic dose : minimally effective dose)
- Minimal cardiovascular and respiratory effects
- No histamine release/hypersensitivity reactions
- No emetic effects

Properties of The Ideal Intravenous Anaesthetic Agent:

Pharmacodynamics properties :

- No involuntary movements
- No emergence nightmares
- No hang over effect
- No adrenocortical suppression
- Safe to use in porphyria


Intravenous Anesthetics
Barbiturates
Benzodiazepines
Opioids
Miscellaneous drugs

Barbiturates (thiopenton or thiopental)

Presentation :

- Supplied as a pale yellow powder.
- Vials commonly contain sodium thiopental with 6% sodium carbonate.
- Reconstituted with water to yields a 2.5% solution (25mg.ml-1) with a pH of 10.8.
- The alkaline solution is bacteriostatic and safe to keep for 48 hours, but make it incompatible with many basic drugs.

Barbiturates (thiopenton or thiopental)

Pharmaceutical :

- A **dose** (**3–6** mg kg-1) of thiopentone produces a smooth onset of hypnosis within **30** seconds of intravenous injection.
- Recovery after a single dose is **rapid** due to **redistribution** and there is a low incidence of restlessness and nausea and vomiting.
- Thiopentone is **65-85%** protein bound in plasma. Metabolism is slow and occurs in the liver. Excretion of metabolites occurs mainly in the urine.
- Repeated doses or infusions of thiopental leading to an **accumulation** of the active drug and **delayed recovery**.

Barbiturates (thiopenton or thiopental)

Indications :

1. Induction of anesthesia (Hypnotic)
2. Maintenance of anesthesia (but has cumulative effects)
3. Treatment of status epilepticus
4. Reduction of intra-cranial pressure (ICP)
5. Brain protection from the effects of hypoxia after stroke and head injury.

Barbiturates (thiopenton or thiopental)

Adverse effects:

1. Hypotension
2. Respiratory depression
3. Tissue necrosis (if injected extra-vascular)
4. Laryngospasm
5. Bronchospasm (avoid in asthma)
6. Thrombophlibitis (less common in 2.5% conc.)

Barbiturates (thiopenton or thiopental)

Adverse effects:

7 - Allergic reactions 1 in 14000-20000

8 - Intra-arterial injection (lead to sever vasospasm and sever pain it may lead to gangrene of the limb, treatment by keeping the cannula in and inject papeverine 20 mg, heparin and fluid, using 2.5% conc. Is safer)

Barbiturates (thiopenton or thiopental)

Contraindications:

1. Airway obstruction (epiglottis or pharyngeal tumours)
2. Porphyria
3. Previous hypersensitivity to this drug

Benzodiazepines (Diazepam, Midazolam)

Indications:

1. Sedation during regional anesthesia
2. Radiological procedures (children, anxious persons)
3. Endoscopy
4. ICU
5. Supplementation to general anesthesia
6. Amnesia
7. Status epilepticus

Benzodiazepines (Diazepam, Midazolam)

Adverse effects:

1. Prolong duration (diazepam)
2. Painful on injection (diazepam)
3. Hypotension if used with other agents like opioids
4. Respiratory depression in over dosage

Contraindications:

- Early pregnancy (teratogenic effect)

Opioids

Agonist
Morphine, Pethidine, Tramadol
Fentanyl & Al, Remi, Su (fentanil)

Agonist-Antagonist
Pentazocine, Nalburphine

Antagonist
Nalaxone

Opioids :

Indications :

1. Provision of analgesia before or after surgery
2. Induction of anesthesia and maintenance of anesthesia in patients with severe cardiac dysfunction
3. Inhibition of reflex sympathetic nervous system activity
4. Provide post operative analgesia by injecting it to the subarachnoid or epidural space

Opioids :

Adverse effects :

1 - On cardiovascular system:

1. Orthostatic hypotension (decreased sympathetic nervous system tone to peripheral veins)
2. Release of histamine (Morphine)
3. Bradycardia (Sufentanil)

Opioids :

Adverse effects :

2 - On Ventilation :

1. Increase resting PaCo2
2. Decrease of responsiveness to the ventilatory stimulation of CO2
3. Decreased rate of breathing but tidal volume is often increased
4. Spasm of thoraco-abdominal muscles

- Stiff chest syndrome

Opioids :

Adverse effects :

2 - On CNS :

1. Miosis
2. Stimulation of Dopamine receptors in the chemoreceptor trigger zone which cause nausea and vomiting
3. Addiction

Opioids :

Adverse effects :

3 - On GIT & Urinary Bladder :

- Enhancement of bladder sphincter tone which
- lead to urine retention
- Decrease peristalsis movement of bowel
- Increase the tone of the pyloric sphincter which
- lead to delayed gastric emptying
- Spasm of biliary smooth muscles which leads to pain also spasm of the sphincter of Oddi

Morphine (10, 15mg)

- Can be Administered by variety of routes
- Has active metabolites
- Risk of accumulation in patient with renal impairment
- Avoid in asthma (histamine release)

Pethidine (100mg)

- Shorter acting
- Its metabolites has long half life with risk of accumulation in patient with renal impairment, also the metabolites are neurotoxic and result in grand mal seizures
- Avoid in patient with history of epilepsy

Tramadol (100mg)

- Analgesic efficacy around one tenth that of morphine
- Avoid in patient with history of epilepsy
- Useful for elderly
- Useful For Patient-Controlled Analgesia (PCA)

Fentanyl (100µg)

- Very potent opioid used primarily for intra-operative analgesia
- Useful drug for PCA
- Cause respiratory depression

Alfentanil (100µg) :

- Ultra short-acting potent opioid used for intra- operative analgesia
- Limited use in the post operative period
- Cause respiratory depression

Sufentanil :

- Is closely related in structure to fentanyl
- 5-10 times more potent than fentanyl and slightly shorter duration

Remifentanil :

- Ultra short acting opioids
- The duration of action is short with no residual effects

Opioids :

Agonist-Antagonist

- Those drugs have limited analgesic properties (ceiling effect) above which increasing doses do not produce additional anesthesia, they usually used for treatment of addiction

Opioids :

Antagonist :

- Is used as a short acting opioid antagonist because of its short duration of action opioid terminated depression may return when effect of Nalaxone have terminated
- **Nalaxone** may precipitate the sympathetic drive of unrelieved pain (tachycardia, hypertension, arrhythmias----- etc.)

Opioids :

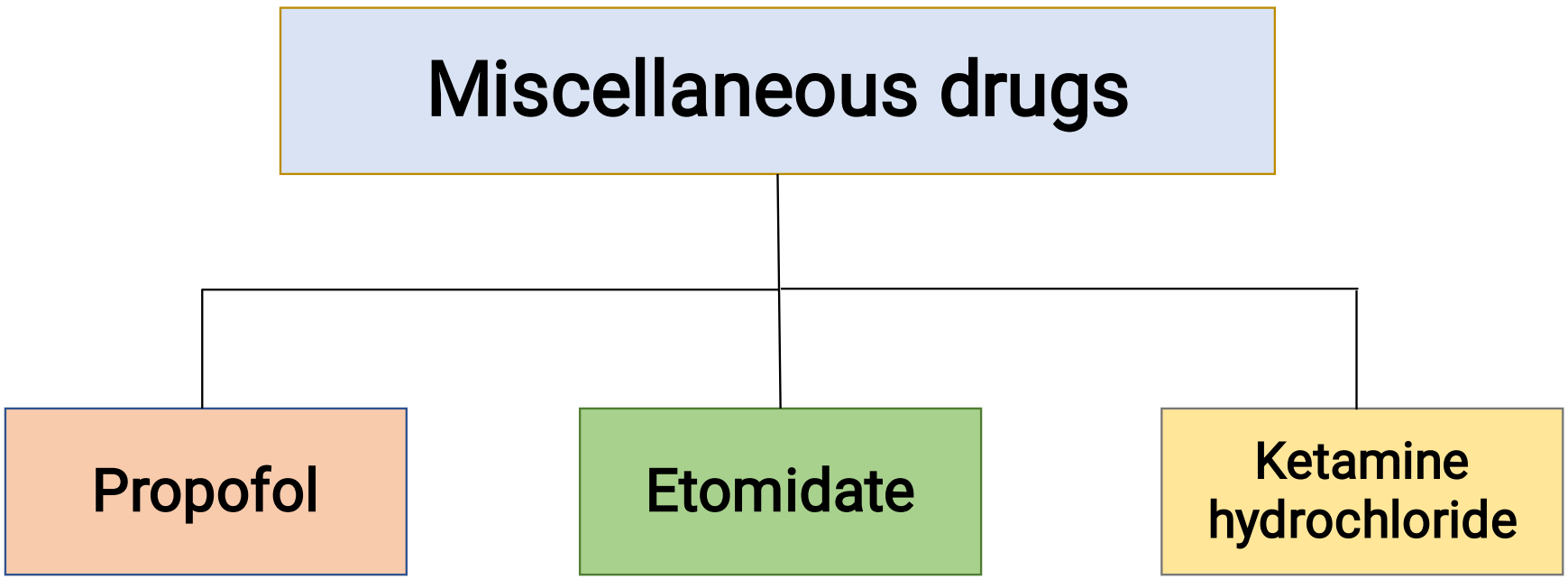
Naloxone

- Naloxone competes with opioids at the mu, delta, kappa and sigma receptors.
- Ampules of 0.02, 0.4 and 1 mg/ml.
- Peak effect 1-2 min.
- Duration of action 30-60 min.
- Used in perioperative surgical patients with excessive sedation or respiratory sedation secondary to opioids.

Opioids :

Naloxone

- Given in small incremental doses.
- High doses of naloxone will result in sudden reversal of analgesic effects leading to abrupt return of pain resulting in hypertension, tachycardia, pulmonary edema, ventricular dysrhythmias and cardiac arrests.
- If sedation or respiratory depression recurs, continuous infusion of 3-10 mcg/kg/hour of naloxone is required.

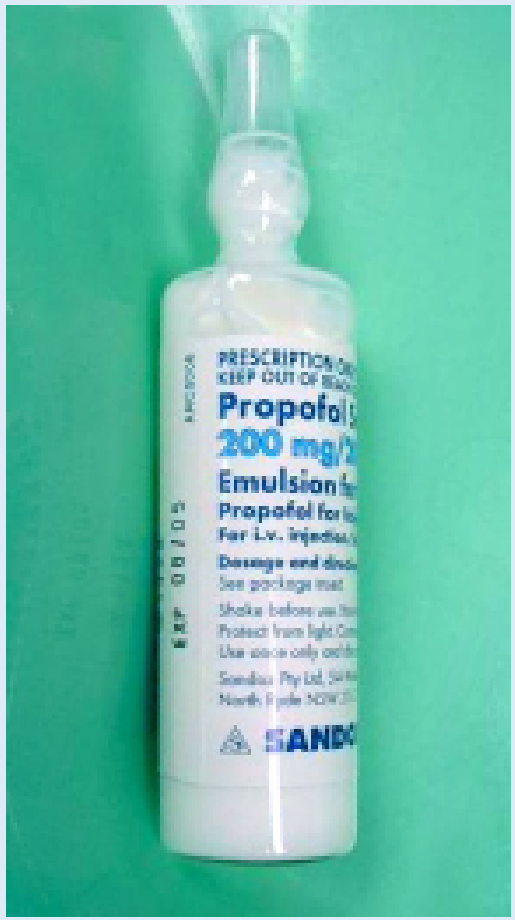

Miscellaneous drugs
Propofol
Etomidate
Ketamine hydrochloride

Miscellaneous drugs :

1 - Propofol :

• Oil-in-water emulsion containing soybean oil, glycerol, and egg lecithin (egg yolk) .

• A history of egg allergy does not necessarily contraindicate the use of propofol because most egg allergies involve a reaction to egg white (egg albumin), whereas egg lecithin is extracted from egg yolk.



Miscellaneous drugs :

1 - Propofol :

• Propofol formulations can support the growth of bacteria, so sterile technique must be observed in preparation and handling and it should be administered within 6 h of opening of ampule

• Postoperative nausea and vomiting appear to be extremely uncommon

Miscellaneous drugs :

1 - Propofol :

Physical and chemical properties

- It’s appearance is similar to that of a 2% milk.
- It has a pH of 7 and is supplied in 20 ml ampoules with a concentration of 10 mg/ml.
- Neither precipitates histamine release nor triggers malignant hyperthermia.
- Has no effects on muscle relaxants.

Miscellaneous drugs :

1 - Propofol :

Effects on Organ systems :

A- Cerebral :

- Decreases cerebral blood flow and intracranial pressure, intraocular pressure
- Induction is occasionally accompanied by excitatory phenomena
- such as muscle twitching, spontaneous movement, opisthotonus, or hiccupping.
- Propofol has antiemetic, antipruritic, and anticonvulsant properties.

B- Cardiovascular:

- Decrease in arterial blood pressure secondary to a drop in systemic vascular resistance, contractility, and preload.(more large doses, rapid injection, & old age.
- Hypotension is more pronounced than with thiopental.
- Propofol markedly impairs the normal arterial baroreflex response to hypotension.

Miscellaneous drugs :

1 - Propofol :

Effects on Organ systems :

C- Respiratory:

- Propofol causes profound respiratory depression. Propofol induced depression of upper airway reflexes exceeds that of thiopental allowing intubation, endoscopy, or laryngeal mask placement in the absence of neuromuscular blockade .
- it depresses the normal response to hypercarbia.
- Although propofol can cause histamine release, induction with propofol is accompanied by a lesser incidence of wheezing in both asthmatic and non-asthmatic patients compared with barbiturates or Etomidate.

Miscellaneous drugs :

1 - Propofol :

Effects on Organ systems :

D- Venous irritation:

- Pain on injection is more common than with thiopental esp.
- If given in a small vein in the hand.
- To solve this problem:

1. small doze of lidocaine with propofol.
2. administering propofol through a fast flowing more proximal IV catheter.

Miscellaneous drugs :

2- Ketamine hydrochloride :

- It’s a dissociative anesthetic agent (mean that the patient is unconscious but appears awake and doesn’t feel pain (cause the patient to appear conscious eg, eye opening, swallowing, muscle contracture)

Miscellaneous drugs :

2- Ketamine hydrochloride :

Physical and chemical properties

- chemically related to the psychotropic drug (e.g. phencyclidine).
- Water soluble, and 10x more lipid soluble than thiopental.
- pH=3.5 - 5.5 (Acidic colorless)

Miscellaneous drugs :

2- Ketamine hydrochloride :

Mechanism of action :

- There are 3 theories explains the MOA of ketamine :

1 – N-methyl aspartate receptor theory :

- NMA receptors may represent a subgroup of the sigma opiate receptors (the PCP site) that blocks spinal pain reflexes

2 – Opiate receptor theory :

- Ketamine may have some affinity for opiate receptors but it’s effect can’t be reversed with naloxone.

3- Miscellaneous receptor theory :

- It reacts with muscarinic, cholinergic and serotonergic receptors.
- Ketamine is a potent analgesic at subanesthetic plasma concentrations.
- It has a wide margin of safety (up to 10x the usual dose)

Miscellaneous drugs :

2- Ketamine hydrochloride :

A - Indications :

1. Shocked patient or patients with cardiovascular collapse requiring emergency surgery
2. Pediatric anesthesia
3. Difficult locations (at accident site, wars)
4. Analgesia And sedation (wound dressing change)
5. In ICU
6. In developing countries (where anesthesia equipment's and trained staff are in short supply)
7. Sole anesthetic for diagnosis and surgical procedures
8. Induction of anesthesia
9. To supplement regional or local anesthetic techniques
10. severe asthmatic pts.

Miscellaneous drugs :

2- Ketamine hydrochloride :

B - Adverse effects :

1. Emergence delirium, nightmares and hallucinations
2. Hypertension and tachycardia
3. Prolong recovery
4. Salivation
5. Increase intra-cranial pressure

Miscellaneous drugs :

2- Ketamine hydrochloride :

Contraindications :

1- lack of knowledge of the drug
2- lack of resuscitative equipment
3- inability to maintain a patent airways
4- allergy to ketamine
5- history of psychosis
6- cerebral-vascular disease
7- Patients. For whom hypertension is hazardous

Miscellaneous drugs :

2- Ketamine hydrochloride :

Pharmacodynamics :

1 – CNS :

1. **ketamine increases cerebral oxygen consumption, cerebral blood flow, and intracranial pressure**
2- generalized increase in the muscle tone and purposful movements.
3- Unpleasant dreams, hallucinations or frank delirium (esp. females & large dose of ketamine).

   incidence of delirium in 15-35 year old Pts is approx. 20%

4- Ketamine comes closest to being a “complete” anesthetic as it induces analgesia, amnesia, and unconsciousness.

Miscellaneous drugs :

2- Ketamine hydrochloride :

Pharmacodynamics :

2 – Respiratory system:

- It preserves laryngeal &pharyngeal airway reflexes.
- Ketamine is a potent bronchodilator.
- FRC → unchanged.
- Minute ventilation → unchanged.
- Tidal volume → unchanged.
- Hypoxic pulmonary vasoconstriction → unchanged.
- Ketamine causes increased secretions but this can be limited by anti-cholinergic drugs.

Miscellaneous drugs :

2- Ketamine hydrochloride :

Pharmacodynamics :

3 – CVS :

- It produces central sympathetic stimulation, which **increases:**

1. Arterial blood pressure, heart rate, and cardiac output.
2. Pulmonary artery pressure.
3. Coronary blood flow.
4. Myocardial oxygen uptake, work.

- It may cause myocardial depression if the sympathetic nervous sys is exhausted or blocked.

Miscellaneous drugs :

3 – Etomidate :

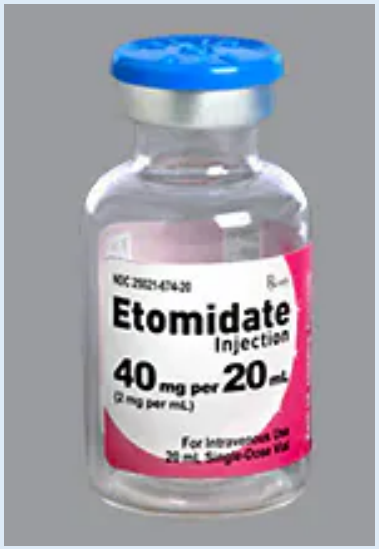
Chemical :

- Etomidate is an imidazole ester.

Presentation :

lipid emulsion

clear solution containing propylene glycol at a concentration of 2mg.ml-1.the pH of aqueous solution is 8.1



Main action :

Hypnotic .

Miscellaneous drugs :

3 – Etomidate :

Clinical use :

- induction of anaesthesia (hypnotic)
- Hemodynamic profile on induction, with minimal blood pressure depression, making it ideal for shock trauma, hypovolemic patients, or patients with significant cardiovascular disease.
- Pharmacokinetics: The onset of action: 30 to 60 seconds, Peak effect: 1 minute
- **Etomidate does not release histamine.**

even in large doses, produces relatively light anesthesia for laryngoscopy

and marked increases in heart rate and blood pressure

Miscellaneous drugs :

3 – Etomidate :

Notes :

- Etomidate does not release histamine.
- Even in large doses, produces relatively light anesthesia for laryngoscopy and marked increases in heart rate and blood pressure
- Has no analgesic effect

Miscellaneous drugs :

3 – Etomidate :

Adverse Effects :

1- Transient inhibition of adrenal steroid synthesis (no longer administered by continuous infusion because of the risks of sustained suppression of endogenous cortisol and aldosterone production) .

2- pain on injection . (Use of Lidocaien)

3- Transient skeletal muscle movements or myoclonus in about 32% of the patients .

4- Postoperative nausea and vomiting .

TABLE 9–3 Uses and doses of ketamine, etomidate, and propofol.

Agent	Use	Route[1]	Dose
Ketamine	Induction	IV	1–2 mg/kg
		IM	3–5 mg/kg
	Sedation[2]	IV	2.5–15 mcg/kg/min
Etomidate	Induction	IV	0.2–0.5 mg/kg
Propofol	Induction	IV	1–2.5 mg/kg
	Maintenance infusion	IV	50–200 mcg/kg/min
	Sedation infusion	IV	25–100 mcg/kg/min

[1]IV, intravenous; IM, intramuscular.

[2]Almost always in combination with propofol.

TABLE 9–4 Summary of nonvolatile anesthetic effects on organ systems.[1]

	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	↓↓	↓↓	↓↓
Ketamine	↑↑	↑↑	↓	↑↑↑	↑↑[2]	↑	↑↑[2]
Etomidate	0	↓	↓	0	↓↓↓	↓↓↓	↓↓↓
Propofol	0	↓↓	↓↓↓	0	↓↓↓	↓↓↓	↓↓↓

[1]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).

[2]Minimal change in CBF and ICP when coadministered with other agents (see text).

TABLE 9–2 Uses and doses of commonly used benzodiazepines.

Agent	Use	Route[1]	Dose (mg/kg)
Diazepam	Premedication	Oral	0.2–0.5[2]
	Sedation	IV	0.04–0.2
Midazolam	Premedication	IM	0.07–0.15
	Sedation	IV	0.01–0.1
	Induction	IV	0.1–0.4
Lorazepam	Premedication	Oral	0.05

[1]IV, intravenous; IM, intramuscular.

[2]Maximum dose is 15 mg.

TABLE 9–1 Uses and dosages of common barbiturates.

Agent	Use	Route[1]	Concentration (%)	Dose (mg/kg)
Thiopental, thiamylal	Induction	IV	2.5	3–6
Methohexital	Induction Sedation Induction	IV IV Rectal (children)	1 1 10	1–2 0.2–0.4 25
Secobarbital, pentobarbital	Premedication	Oral IM Rectal suppository	5	2–4[2] 2–4[2] 3

[1]IV, intravenous; IM, intramuscular.

[2]Maximum dose is 150 mg.

TABLE 10–3 Uses and doses of common opioids.

Agent	Use	Route[1]	Dose[2]
Morphine	Postoperative analgesia	IM IV	0.05–0.2 mg/kg 0.03–0.15 mg/kg
Hydromorphone	Postoperative analgesia	IM IV	0.02–0.04 mg/kg 0.01–0.02 mg/kg
Fentanyl	Intraoperative anesthesia Postoperative analgesia	IV IV	2–50 mcg/kg 0.5–1.5 mcg/kg
Sufentanil	Intraoperative anesthesia	IV	0.25–20 mcg/kg
Alfentanil	Intraoperative anesthesia Loading dose Maintenance infusion	 IV IV	 8–100 mcg/kg 0.5–3 mcg/kg/min
Remifentanil	Intraoperative anesthesia Loading dose Maintenance infusion Postoperative analgesia/sedation	 IV IV IV	 1.0 mcg/kg 0.5–20 mcg/kg/min 0.05–0.3 mcg/kg/min

[1]IM, intramuscular; IV, intravenous.

[2]Note: The wide range of opioid doses reflects a large therapeutic index and depends upon which other anesthetics are simultaneously administered. For obese patients, dose should be based on ideal body weight or lean body mass, not total body weight. Tolerance can develop rapidly (ie, within 2 h) during IV infusion of opioids, necessitating higher infusion rates. Dose correlates with other variables besides body weight that need to be considered (eg, age). The relative potencies of fentanyl, sufentanil, and alfentanil are estimated to be 1:9:1/7.

TABLE 10–1 Classification of opioid receptors.[1]

Receptor	Clinical Effect	Agonists
μ	Supraspinal analgesia (μ_1) Respiratory depression (μ_2) Physical dependence Muscle rigidity	Morphine Met-enkephalin[2] β-Endorphin[2] Fentanyl
κ	Sedation Spinal analgesia	Morphine Nalbuphine Butorphanol Dynorphin[2] Oxycodone
δ	Analgesia Behavioral Epileptogenic	Leu-enkephalin[2] β-Endorphin[2]
σ	Dysphoria Hallucinations Respiratory stimulation	Pentazocine Nalorphine Ketamine

[1]Note: The relationships among receptor, clinical effect, and agonist are more complex than indicated in this table. For example, pentazocine is an antagonist at μ receptors, a partial agonist at κ receptors, and an agonist at σ receptors.

[2]Endogenous opioid.

Drug Name	Mechanism of action	Absorption	Distribution	Biotransformation (Metabolism)	Excretion	Notes
Midazolam	GABA Receptor Antidot : Flumazenil	IV	Water Soluble		Renal (urine)	
Diazepam		GIT more than IM – IV (pain full on injection)	Lipid Soluble	Liver (Lipid to water soluble)	Renal (urine)	Active metabolite 30 Hrs
Lorazepam		Oral			Renal (urine)	
Propofol	GABA Receptor	IV	oil-in-water emulsion **not water soluble**	Extrahepatic Conjugation in the liver results in inactive metabolites	Renal (urine)	
Ketamine	(**NMDA**) receptor **antagonist**.	Oral – Nasal – Rectal IV – IM (10 – 15 min) SC – Epidural	More Lipid Soluble less proten bound than Thiopental	Liver (nor ketamine) active metabolic	Renal (urine)	Action (10 – 15 min)
Itomidate		IV		Liver by ester hydrolysis to inactive metabolic	75 % Urine, Bile	

Drug Name	Mechanism of action	Absorption	Distribution	Biotransformation (Metabolism)	Excretion
Thiopental	Depress (RAS) on the brainstem - potentiate the action of GABA	IV Rectal sometime in cheldrin	Lipid Soluble and 60 % high nonionized fraction and rapid brain uptake (30 sec)	Liver to **inactive** water-soluble metabolites.	Urine

Notes :

The **duration of sleep** doses of the thiopental is determined by **redistribution,** not by metabolism or elimination

Pt lose consciousness within **30 s** and awaken within **20 min**

Induction dose of thiopental will ***depend on*** body **weight** and **age**.

Reduced for **elderly patients** due to **slower redistribution.**

(RAS) Reticular Activating System

(GABA) Gamma Amino Butaric Acid

Thank You

End of lecture