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Intravenous Anesthetic Agents

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<tr><th colspan="4">1- Barbiturates (Thiopental)</th></tr>
<tr><th>Agent</th><th>Notes</th><th>Effects</th><th>Uses and Side Effects</th></tr>
<tr>
<td rowspan="2">Sodium Thiopental (Pentothal)</td>
<td>- It's a yellow powder with a sulphuric smell and a bitter taste.
- Highly lipid soluble compound
- Dosing: 3-5 mg/kg and within 30-60 secs after administration, the "arm brain" circulation time is met.
- Anesthetic state persists for 5-10 mins (Ultra short)
Pharmacokinetics
- Albumin-bound (75%)
- NSAIDS may displace thiopental from albumin causing acidosis.
- Liver & renal disease may be associated with low albumin levels which results in an increase in free thiopental → toxicity
- Short duration of action.
- Metabolism: primarily in the liver with approx. 10-15% of the drug level metabolized per hour.
- Less than 1% of the drug is excreted unchanged in the urine.</td>
<td><u>CVS</u>
- Dose-dependent reduction in CO, SV, and BP → may provoke 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.

<u>Respiratory</u>
- Dose-dependent respiratory depression
- FRC is reduced by 20% with induction of anesthesia
- It may produce a degree of laryngospasm and bronchospasm.

<u>CNS</u>
reduction in cerebral oxygen consumption, blood flow, blood volume and cerebrospinal fluid pressure →reduces ICP – at high doses

<u>Renal</u>
Increase in ADH → decrease U/O</td>
<td><u>Uses</u>
- Induction and maintenance of anesthesia for short procedures.
- Control of convulsive states
- To supplement regional anesthesia.

<u>Side Effects</u>
- Hypotension esp. in hypovolemic, shocked ones.
- Respiratory depression in excessive doses
- Tissue necrosis.
- Laryngo- and bronchospasm in asthmatics pts.
- Allergic reactions: from coetaneous rashes to severe anaphylactic shock.
- Intra-Arterial injection can rarely lead to ischemia and pain.
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 procaine and analgesia.</td>
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<tr><td colspan="3"></td></tr>
<tr><th colspan="4">2- Non-Barbiturates (Propofol, Etomidate, Ketamine, Benzodiazepine)</th></tr>
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<td>Fospropofol</td>
<td colspan="3">- Approved 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
- 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 is not affected by race, sex, mild to moderate renal impairment, age, or alkaline phosphatase concentration.
- No pharmacokinetic interactions have been found between Fospropofol and fentanyl, midazolam, morphine, or propofol. It is not subject to cytochrome P450 enzyme-mediated metabolism
- It is not associated with pain on injection, unlike propofol. Only mild to moderate perineal paresthesia and pruritus minutes after a bolus injection.</td>
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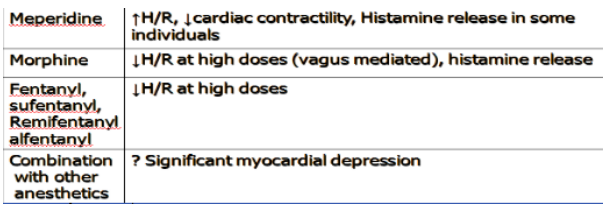
Agent	Notes	Pharmacokinetics	Uses and Side Effects
Propofol	- Drug of choice for most patients. - For induction and maintenance of anesthesia and for sedation in and outside the operating room. - MOA: activation of $GABA_A$ receptor complex + antagonist of the (NMDA) receptor. - Highly lipid soluble. - It is a weak organic acid with a pKa = 11 so that it is almost entirely unionized at pH 7.4. - **Dosing**: 1-2.5 mg/kg, reducing the initial dose and titrating propofol in increments in older age / hypovolemia or myocardial dysfunction **Propofol infusion syndrome** - A rare but lethal syndrome where infusion of propofol at >4 mg/kg/hour for 48 hours or longer causes acute refractory bradycardia leading to asystole in the presence of one or more of the following: ✓ metabolic acidosis ✓ rhabdomyolysis ✓ hyperlipidemia ✓ enlarged or fatty liver - Other manifestations include cardiomyopathy with AHF, skeletal myopathy, hyperkalemia, hepatomegaly, and lipemia.	- 98% protein bound to albumin - Largest volume of distribution of all the induction agents. - Highly lipid-soluble, resulting in very rapid onset. 1.5 - 2.6 minutes (arm brain circulation). - Its duration of action is short - Propofol is oxidized and conjugated in the liver. Metabolites are inactive. - Excreted by the kidneys. - The clearance of propofol is extremely high. Renal metabolism accounts for up to 30% of propofol clearance, (lungs also 20 to 30%). - 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%); should be 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%). Competitive inhibition of cytochrome P450 system activity → competition of propofol and midazolam.	**Advantages** - Rapid onset (30 to 45 seconds) and recovery - Antiemetic and antipruritic properties (for patients who will receive opioids, which often cause pruritus). - Bronchodilatory properties with decreased airway resistance. - Anticonvulsant properties. - Suitable for patients with renal and/or hepatic insufficiency **Side Effects** - Dose-dependent hypotension. HR is minimally affected while systolic BP decreases to <90 mmHg in 16% of patients → take care in hypovolemic or hemodynamically compromised, as well as in older patients. - Dose-dependent respiratory depression - Pain on injection. Typically, lidocaine and/or an opioid is co-administered. Eliminated or reduced in hemodynamically instable patient. Injection of propofol into a larger or central vein also minimizes pain. - Contamination risk. 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 propofol after six hours - Rare allergic reaction. It does not appear to cause any adverse effects when given intraarterially, although onset of anesthesia is delayed.
	Effects		
	RS - Can lead to apnea - Rarely cause laryngospasm → used in anesthesia for ease of placement of a laryngeal mask	**CNS** - Causes dystonic movements with choreiform elements and opisthotonos. - Used to control status epilepticus	**Others** - Fat overload syndrome - causes hyperlipidemia - It may turn urine and hair green. - It's anti-pruritic.

Agent	Notes	Uses and Side Effects
Etomidate	- An imidazole derivative that acts direct on $GABA_A$ receptor complex (increase affinity), blocking neuro-excitation, and producing anesthesia / amnesia / but no analgesia. - Rapid onset without changes in BP, CO, or HR (most hemodynamically neutral agent). - Commonly used in the emergency setting as part of a rapid sequence induction or for conscious sedation - **Dosing**: 0.15 - 0.3 mg/kg IV / 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 - 12 minutes). - The volume of distribution is 2.5 to 4.5 L/kg. - Clearance 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. It does not cause vasodilation or myocardial depression and does not increase sympathetic tone. Thus, BP and HR remain stable. - Most favorable therapeutic index. - Anticonvulsant properties. - It decreases $CMRO_2$, CBF and ICP. Thus, it may be advantageous in hemodynamically unstable patients with head injury or stroke. **Side Effects** - A high incidence 30% of postoperative nausea and vomiting (PONV) compared with propofol. - Pain on injection, 80% of patients, due to venous irritation. Inject into a larger or central vein OR co-administer 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 instable pts). - Absence of any analgesic effect. - It does 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. 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.

Agent	Notes	Pharmacokinetics	Uses and Side Effects
Ketamine	**MOA:** - Blocking polysynaptic reflexes in the spinal cord and inhibiting neurotransmitter effects in selected areas of the brain - It dissociates the thalamus from the limbic cortex (profound analgesia while appearing disconnected from surroundings) - Noncompetitive antagonism of glutamate (NMDA) receptor antagonist - It 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. - It 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. - Co-administered with other adjuvant have additive or infra-additive (antagonistic) rather than synergistic effects. - **Lower initial dose in cases of:** ✓ 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	- Very rapid speed of onset. Arm brain circulation of <1 minute. (15 to 30 minutes in IM). - The primary metabolite (by liver) of ketamine is norketamine. It 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 volume of distribution is 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	**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 maintaining 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 interaction** - 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 (e.g., 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.

Agent	Notes	Pharmacokinetics	Effects
Benzo-diazepines **(Diazepam, Midazolam, Lorazepam 'not for children')**	- Interact with specific receptors in the CNS mainly in the cortex - Binding to receptors (different site) enhances the inhibitory effects of various neurotransmitters (GABA). - 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.	- Administered orally, IM, and IV for sedation or induction of anesthesia - Diazepam and Lorazepam are 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 glucuronide end products - Slow hepatic extraction, long half-life for diazepam (30h) - Metabolites are excreted mainly in the urine. - Enterohepatic circulation produces a second peak in diazepam plasma concentration 6-12h following administration	**CVS** - Minimal depressant effects - Arterial BP, Cardiac output, and PVR slightly decrease - Heart rate sometimes increase **Respiratory** - Depresses ventilatory response to CO_2 → Ventilation must be monitored **Cerebral** - Reduces cerebral oxygen consumption - Decreases cerebral blood flow and ICP - Effective in preventing and controlling grand mal seizures - Sedative dosages cause antegrade amnesia
3- Others (Dexmedetomidine, Opioids)			
Dexmedeto-midine	- It is a sedative medication used by intensive care units and anesthesiologists, - Unique in that it sedates without causing respiratory depression - **MOA**: agonism of alpha-2 receptors in certain parts of the brain. - It 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. It also has an opioid sparing effect. - Metabolized in the liver and metabolites eliminated in the urine - Side effects include bradycardia, heart block and hypotension		

Agent	Notes	Pharmacokinetics	Effects
Opioids	- "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 stereo-specifically antagonized by Naloxone - **MOA**: interaction with Specific opioid receptors in the CNS (brain and Spinal Cord) and peripheral tissues (somatic and sympathetic nerves) / Modifying how pain is perceived **Opioid Receptors:** ✓ μ (mu): with μ-1 and μ-2 subtypes ✓ Κ (kapa) ✓ б (delta) ✓ σ (sigma) - 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. Acetylcholine, substance P).	- Distribution half-lives of all opioids are rapid: 5-20 minutes. - Most opioids depend on the liver for biotransformation, with high hepatic extraction ratio. - Excretion of end products of opioids metabolism is mainly through the kidney. - Morphine has low fat solubility accounting for its slow onset and prolonged duration of action. It has both active and inactive metabolites. 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. - Pethidine (Meperidine) is metabolized to the active normeperidine. Normeperidine has an excitatory effect on CNS leading to Myoclonic activity and seizures that are not reversed by Naloxone. - Remifentanil has a unique ester structure ➔ rapid ester hydrolysis: terminal elimination half-life of 10 minutes. - 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.	**Respiratory** - 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, alfentanil. - 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 **CVS** 

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).