Intravenous anesthetics

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The triad of balanced general anaesthesia

Unconsciousness (1)

Analgesia (2)  (3) Muscle relaxation
Function of intravenous anaesthetic agents

• Rapid induction of anaesthesia

• Maintenance of anaesthesia

• ICU/theatre sedation

• Status epilepticus
Pharmacokinetics

• Agent has to cross the BBB

• Speed of action depends upon;
  – Lipid solubility
  – Protein binding
  – Speed of injection
  – Cardiac output
The ideal intravenous agent

- Rapid onset
- Rapid recovery
- Analgesic
- No CVS/RS depression
- No emetic effects
- No excitatory phenomena
- No pain on injection
- Safe if injected intra-arterially
- None toxic to other organs
- No histamine release
- No allergic reactions
- Water soluble
- No stimulation of porphyria
Compartment Model

• Offers a simple way to characterize the distribution of drugs in the body

• Distribution phase vs. Elimination phase
Redistribution and elimination of intravenous anaesthetic agents

Redistribution to vessel rich group

Redistribution to muscle/fat

Elimination

[Plasma Conc.]
General anesthetics

Inhaled
- Gas (nitrous oxide)
- Volatile liquids (halothane)
- Barbiturates (thiopental)

Intravenous
- Benzodiazepines (midazolam)
- Dissociative (ketamine)
- Opioids (fentanyl)
- Miscellaneous (etomidate, propofol)

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Barbiturates
(SODIUM THIOPENTAL)

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

- Oxybarbiturates ➔ methohexital
- Thiobarbiturates ➔ thiopental, thiamylal
Mechanism of action

**Thiopental**

- Depress the reticular activating system *(ras)* located in the brain stem that controls several vital functions, consciousness
- Affect the function of nerve *synapses* not *axons*
- Interact with the inhibitory neurotransmitter *GABA*.
- Dose **3-5 mg/kg**
- Thiopental is highly protein bound (80%)
Thiopental

• Redistribution
Effect on organ systems

Cardiovascular

• **BP and HR** → **maintain CO**
• Depression of the medullary vasomotor center **vasodilates peripheral capacitance vessels**, increases peripheral pooling of blood and decreases venous return to right atrium

Respiratory

• **Depresses** the medullary ventilatory center and decreases the ventilatory response to hypercapnia and hypoxia
• **Tidal volume and respiratory rate**
• **Histamine release** and bronchial smooth muscle constriction → bronchospasm
Effect on organ systems

Cerebral

- Constrict the cerebral vasculature and cause decrease in cerebral blood flow and intracranial pressure
- **Cerebral perfusion pressure increases** cause the drop in ICP exceeds the drop in arterial BP
- Decreases cerebral oxygen consumption (up to 50%)
- Have anti-analgesic effect by lowering the pain threshold
Effect on organ systems

Renal
- renal blood flow and GFR in proportion to fall in BP

Hepatic
- hepatic blood flow
- Induction of hepatic enzymes, increases the rate of metabolism of some drugs (Digitoxin)
- Combination with the cytochrom p-450 enzyme system interfere with biotransformation of some drugs (TCA)
Thiopental

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

- **Contraindications**
  - Airway obstruction
  - Porphyria
  - Hypersensitivity
Etomidate

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

• Administered **IV only for induction of GA**

Distribution

• High protein bound and high lipid soluble
• Redistribution is responsible for decreasing the plasma concentration to awakening level

Biotransformation and excretion

• Hepatic microsomal enzymes and plasma esterases
• excreted in the urine
Effect on organ systems

Cardiovascular

• **Minimal effect on CVS**
• Mild reduction in PVR and arterial BP
• Myocardial contractility and cardiac output are unchanged
• No histamine release

Respiratory

• Ventilation is affected less than barbiturates
Effect on organ systems

Cerebral

• cerebral metabolic rate, cerebral blood flow, and ICP
• Post op. N-V are common but minimized by antiemetic

Endocrine

• Inhibit enzymes involved in cortisol and aldosterone synthesis
• Can lead to adrenocortical suppression in the long run
Side effects

• May activate seizure, extrapyramidal activity.
• Pain on injection.
• Adrenocortical suppression.
• Allergic reactions.
• Post op. nausea and vomiting.
Ketamine

- Has multiple effects through the CNS.
- Ketamine dissociates the thalamus from the limbic cortex (dissociative anesthesia)
  - Causes the pt to appear conscious but unable to process or respond to sensory input.
- N-methyl-D-aspartate (NMDA) receptor antagonist
- Structurally analogue to phencyclidine
- Can cause hallucinogenic effects and nightmares
- Dose: Induction IV 1-2 mg/kg ... IM 3-5 mg/kg
Distribution
• More lipid soluble and less protein bound than thiopental
• Distribution half-life is 10-15 min

Biotransformation and excretion
• Biotransformed in the liver to several metabolites some retain anesthetic properties (norketamine)
• Short elimination half-life (2h)
• Excreted renally
Effect on organ systems

Cardiovascular
- BP, HR, and CO
- Pulmonary artery pressure and myocardial work
- Avoid in patient with coronary artery disease

Respiratory ....
- Minimal effect on the ventilatory drive
- Potent bronchodilator
- Preserve airway reflexes

......rs stimulation
Effect on organ systems

Cerebral

- Increased cerebral oxygen consumption, cerebral blood flow and intracranial pressure
- **Myoclonic activity** is associated with increased subcortical electrical activity
- Undesirable psychotomimetic effects *(illusions, dreams and delirium)*
- Have analgesic effects
propofol

Facilitate inhibitory neurotransmitters mediated by GABA Propofol (2,6-diisopropylphenol) consist of phenol ring with two isopropyl groups attached. It is an IV sedative/hypnotic used for induction and or maintenance of anesthesia. It has replaced thiopental as the first choice for induction of GA. Formulation can support bacterial growth (soybean oil, glycerol, and egg lecithin). Dose: induction IV 1.5-2.5 mg/kg. Not water soluble.
• Indication
  – Induction of anesthesia
  – Sedation
  – Maintenance of anesthesia
  – Antiemetic
  – Antipruritic
  – Anticonvulsant
  – Attenuation of bronchoconstriction
Absorption
• Available only for IV for induction of GA and sedation

Distribution
• High lipid soluble with an onset of action as one-arm-to-brain circulation time
• Very short initial distribution half-life (2-8 min)

Biotransformation and excretion
• Clearance exceeds hepatic blood flow with extrahepatic metabolism
• Conjugation in the liver with inactive metabolites as an end product that are eliminated by the kidney
Effect on organ systems

Cardiovascular
- Decrease BP due to drop in systemic vascular resistance, cardiac contractility and preload
- Impairs the normal arterial baroreflex response to hypotension

Respiratory
- It is a respiratory depressant causes apnea following induction dose
- Inhibits hypoxic ventilatory drive and depresses the normal response to hypercarbia
- Can produce bronchodilation and decrease the incidence of wheezing intraoperatively.
Effect on organ systems

Cerebral

• Decreases cerebral blood flow and intracranial pressure
• Autoregulation and response to CO2 are not affected
• Can cause critical reduction in CPP in patients with elevated intracranial pressure (< 50 mm Hg)
• Has antipruritic effect and antiemetic properties
• Have predominantly anti-convulsant properties
• Decreases intraocular pressure
Side effects

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

- Binding to receptors enhances the inhibitory effects of various neurotransmitters (GABA) in the CNS mainly in the cortex.

- Chemical structure includes a benzene ring and a 7-member diazepine ring, substitution at various positions on these rings affect potency and biotransformation.

- Flumazenil is a specific benzodiazepine-receptor antagonist that effectively reverses most of the CNS effect.
Absorption

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

Distribution

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

• Rely on the liver for transformation into water-soluble glucuronide end products
• Slow hepatic extraction, long half-life for diazepam (30h)

Excretion

• Metabolites are excreted mainly in the urine
• Enterohepatic circulation produces a second peak in diazepam plasma concentration 6-12h following administration
Effect on organ systems

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

**Respiratory**
- Depresses ventilatory response to CO2
- Ventilation must be monitored
Effect on organ systems

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
Diazepam

• Often used as premedication or seizure activity, rarely for induction
• Minimal systemic effects-- respirations decreased with narcotic usage
• Not water soluble-- venous irritation(propylene glycol )
• Metabolized by liver-- not redistributed
Lorazepam

• Slower onset of action (10-20 minutes)—not used for induction
• Used as adjunct for anxiolytic and sedative properties
• Not water soluble—venous irritation
Midazolam

- More potent than diazepam or lorazepam
- Induction slow, recovery prolonged
- May depress respirations when used with narcotics
- Minimal cardiac effects
- Water soluble
<table>
<thead>
<tr>
<th>Agent</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>Cerebral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>MAP</td>
<td>Vent</td>
</tr>
<tr>
<td>Barbiturates</td>
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<td></td>
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</tr>
<tr>
<td>Thiopental</td>
<td>↑↑</td>
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<tr>
<td>Thiamylal</td>
<td>↑↑</td>
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<tr>
<td>Methohexital</td>
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<tr>
<td>Benzodiazepines</td>
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<tr>
<td>Diazepam</td>
<td>0/↑</td>
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<tr>
<td>Lorazepam</td>
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<tr>
<td>Midazolam</td>
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<tr>
<td>Ketamine</td>
<td>↑↑</td>
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<tr>
<td>Etomidate</td>
<td>0</td>
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<td>↓</td>
</tr>
<tr>
<td>Propofol</td>
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## Properties of Intravenous Anesthetic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Induction and Recovery</th>
<th>Main Unwanted Effects</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>thiopental</td>
<td>Fast onset (accumulation occurs, giving slow recovery) Hangover</td>
<td>Cardiovascular and respiratory depression</td>
<td>Used as induction agent declining. Decreases cerebral blood flow and O2 consumption. Injection pain</td>
</tr>
<tr>
<td>etomidate</td>
<td>Fast onset, fairly fast recovery</td>
<td>Excitatory effects during induction and recovery, Adrenocortical suppression</td>
<td>Less cardiovascular and respiratory depression than with thiopental, Injection site pain</td>
</tr>
<tr>
<td>propofol</td>
<td>Fast onset, very fast recovery</td>
<td>Cardiovascular and respiratory depression. Pain at injection site.</td>
<td>Most common induction agent. Rapidly metabolized; possible to use as continuous infusion. Injection pain. Antiemetic</td>
</tr>
<tr>
<td>ketamine</td>
<td>Slow onset, after-effects common during recovery</td>
<td><strong>Psychotomimetic effects</strong> following recovery, Postoperative nausea, vomiting and salivation</td>
<td>Produces good analgesia and amnesia. No injection site pain</td>
</tr>
<tr>
<td>midazolam</td>
<td>Slower onset than other agents</td>
<td>Minimal CV and respiratory effects.</td>
<td>Little respiratory or cardiovascular depression. No injection pain. Good amnesia.</td>
</tr>
</tbody>
</table>
Because of their analgesic property. They're commonly combined with other anaesthetics. The choice of opioid is based primarily on the duration of action needed. The most commonly used is fentanyl because it induce analgesia more rapidly than morphine, while morphine provides long lasting analgesia.
Rapid distribution
Metabolized by liver
Majority of inactive metabolites eliminated unchanged in urine
Opoids

- Opoids bind to specific receptors located throughout CNS

**Table 1**

<table>
<thead>
<tr>
<th>OPIOID RECEPTORS</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Mu₁</td>
<td>Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential</td>
</tr>
<tr>
<td>Mu₂</td>
<td>Respiratory depression, cardiovascular and gastrointestinal effects, miosis, urinary retention</td>
</tr>
<tr>
<td>Delta</td>
<td>Spinal analgesia, cardiovascular depression, decreased brain and myocardial oxygen demand</td>
</tr>
<tr>
<td>Kappa</td>
<td>Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system</td>
</tr>
</tbody>
</table>

Adapted from references 2 and 3.
Effects on organ system

CNS sedate by interfering with sensory perception of painful stimuli
Incapable of producing anaesthesia
May produce nausea and emesis through stimulation of chemoreceptor trigger zone
CVS

Little myocardial depressant even when administered in high doses. Supplementation with either N2O or benzodiazepines may depress CO decrease systemic vascular resistance: decrease sympathetic outflow or releasing histamine. They produce bradycardia by stimulation of vagal nucleus in the brain stem.
GI decrease GI mobility (cause constipation or post op. ileus) + increase biliary tone (biliary colic in bile stone pt.) Urinary increase tone of bladder sphincter (urinary retention) Others anaphylactic reactions, bronchospasm, chest wall rigidity
Narcotic antagonist

Naloxone competes with opioids at the mu, delta, kappa receptors. Used in perioperative surgical patients with excessive sedation or respiratory depression secondary to opioids. Peak effect in 1-2 min. Duration of action 30-60 min. Given in small gradual doses; high doses will result in sudden reversal of analgesic effect.
Thank you

"Your insurance company wouldn't cover anesthesia, but they did buy the medical staff earmuffs to protect our ears for your screaming."