Intravenous anesthetics

Alaa aloqaily
Farah hjooj
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
General anesthetics

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

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

- ↑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
Indications:
1-anesthetic for diagnosis and surgical procedures
2-induction of anesthesia
3-supplement regional or local anesthetic techniques
4-for anesthetic induction in severe asthmatic pts. Or patients with cardiovascular collapse requiring emergency surgery

Contraindications:
1-lack of resuscitative equipment
2-inability to maintain a patent airways
3-allergy to ketamine
4-history of psychosis
5-cerebro-vascular disease
6-Patients for whom hypertension is hazardous
PROPOFOL

Propofol is an intravenous sedative agent used in the induction and maintenance of anesthesia, it is non-analgesic.

Mechanism of action: facilitation of inhibitory neurotransmission mediated by GABAa receptor binding

Physical & chemical properties:
- highly lipid soluble oil
- combined with glycerol, egg, and soya bean oil (1% propofol 10mg/ml, 10% soya bean oil, 2.25% glycerol, 1.2% purified egg phosphatide)
- It has a pH of 7
- Has no effects on muscle relaxants
- low incidence of nausea & vomiting
- Neither precipitates histamine release nor triggers malignant hyperthermia
- Propofol formulations can support the growth of bacteria, so sterile technique must be observed in preparation and handling
Dosage:

<table>
<thead>
<tr>
<th></th>
<th>Induction</th>
<th>Maintenance infusion</th>
<th>Sedation infusion</th>
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<tbody>
<tr>
<td>Propofol</td>
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<tr>
<td>Elderly patients &lt;= 1 mg/kg</td>
<td>IV</td>
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<td>1–2.5 mg/kg</td>
<td>50–200 mcg/kg/min</td>
<td>25–100 mcg/kg/min</td>
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</table>
Effects on different organ systems:

- **Cerebral:**
  1. decreases cerebral blood flow and intracranial pressure.
  2. has antiemetic, antipruritic, and anticonvulsant properties.

- **Cardiovascular:**
  1. decrease systemic vascular resistance $\rightarrow$ decrease BP (Hypotension is more pronounced than with thiopental)
  2. decrease contractility and preload
  3. impairs the normal arterial baroreflex response to hypotension

- **Respiratory:**
  1. profound respiratory depression
  2. depression of upper airway reflexes exceeds that of thiopental

- **Venous irritation:**
  Pain on injection (more than thiopental)
Indications:
1- Initiation and maintenance of Monitored Anesthesia Care sedation → adults only
2- Combined sedation and regional anesthesia → adults only
3- Induction of General Anesthesia → Patients ≥ 3 years of age
4- Maintenance of General Anesthesia → Patients ≥ 2 months of age
5- ICU sedation of intubated, mechanically ventilated patients → adults only

Contraindications:
1- Egg allergy
2- Lack of resuscitation equipment or knowledge of the drug
3- Inability to maintain a patent airway
4- Conditions in which reduction in blood pressure can’t be tolerated (such as aortic or mitral stenosis, tamponade & shock)
Narcotic agonists
Opium derived from dried poppy plant juice, which contain more than 20 plant alkaloids, including morphine and codeine.

- Rapid distribution
- Metabolized by liver
- Majority of inactive metabolites eliminated unchanged in urine

Poppy plant
Opioid receptors

1. Mu receptors (μ): analgesia, respiratory depression, euphoria, & physical dependence.
2. Kappa receptors (K): analgesia, sedation, respiratory depression, miosis.
3. Segma receptors(a): dysphoria, hallucination, tachypnea, tachycardia.

And these receptors located in

1. Brain stem (amygdala, corpus striatum, periaqueductal gray matter and medulla).
   2. Spinal cord(substantia gelatinosa).
3. GIT.
Opioids

- Opioids bind to specific receptors located throughout CNS

<table>
<thead>
<tr>
<th>OPIOID RECEPTORS</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mu&lt;sub&gt;1&lt;/sub&gt;</strong></td>
<td>Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential</td>
</tr>
<tr>
<td><strong>Mu&lt;sub&gt;2&lt;/sub&gt;</strong></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.
CNS
Sedate by interfering with sensory perception of painful stimuli

incapable of producing anesthesia and it can’t guarantee total amnesia.

may produce nausea & emesis through stimulation of the chemoreceptor trigger zone.
CVS

little myocardial depressant effect even when administered in high doses.

Supplementation with either N2O or benzodiazepines may depress cardiac output.

decrease systemic vascular resistance by:
  - decrease sympathetic outflow
Or – releasing histamine (synthetic opioids less likely to release histamine)

They produce bradycardia by stimulation of vagal nucleus in the brain stem.
RS

1- dose related depression of respiratory rate and minute ventilation
2- increase the tidal volume
3- slow deep respiration
GI
Decrease GI mobility, which cause constipation or post op. ileus
Increase biliary tone >> biliary colic in bile stone pt.

Urinary
Increase the tone of bladder sphincter >> urine retention

Others
Anaphylactic reactions, bronchospasm, chest wall rigidity and pruritis.
Morphine

• Is the major analgesic drug contained in the opium in the seedpod poppy plant (natural opioid) and is a strong mu receptor agonist

• Morphine has higher affinity for Mu receptor than others, by the action on Mu receptors, it inhibits the release of several different neurotransmitters including noradrenaline, acetylcholine and substance P

• Duration of action 6-8hrs
Dosage

- Oral; 10 to 30 mg 4 hrly.
- IM SC; 5 to 20 mg 4hrly
- IV; initial dose is 4 to 10 mg slowly over 4 to 5 min 4 hrly
- Pediatric IV 0.025-0.1 mg/kg
- Epidurally 5mg – pain relief up to 24 hrs
- Intrathecally 0.2 to 1 mg
Actions

• 1\ analgesia
  • By raising the pain threshold at the spinal cord level and by altering the brain perception of pain

• 2\ euphoria
  • Caused by disinhibition of the dopamine-containing neurons
• 3\respiration depression
  • By reduction of the sensitivity of respiratory center neurons to carbon dioxide, accentuated as the dose is increased
  • It’s the most common cause of death in acute opioid overdoses

• 4\depression of cough reflex
  • Antitussive properties
• 5\miosis
• By stimulation of M and K receptors “this is important diagnostically, because many other causes of coma and respiratory depression produce dilatation of the pupil

• 6\emesis
• Directly stimulates the chemoreceptors trigger zone in the area postrema that causes vomiting
• GI tract
  • Relieves diarrhea by decreasing the motility and increasing the tone of the intestinal smooth muscle
  • Also increases the tone of anal sphincter
  • Morphine and other opioids produce constipation with little tolerance developing
  • Laxative combination of stool softener docusate with the stimulant laxative senna is useful to treat opioid-induced constipation
  • Increase biliary tract pr. Due to contraction of gallbladder and constriction of biliary sphincter
• 8\ CVS

• at lower doses no major effects on blood pressure or heart rate, with large doses HOTN and bradycardia may occur

• Because of respiratory depression and CO2 retention, cerebral vessels dilate and increase cerebrospinal fluid pr. Therefore, morphine is usually contraindicated in patient with head trauma or severe brain injury
• **9\histamine release**
  • Histamine release from mast cells causing urticaria, sweating and vasodilation
  • Because it can causes bronchoconstriction, morphine should be used with caution in patients with asthma

• **10\ urinary retention**
  • It increases antidiuretic hormone
  • ?

• **11\ labor**
  • May prolong the second stage of labor by transiently decrease the strength, duration and frequency of uterine contractions (shouldn’t be used as analgesia during labor)
Administration

• IM, IV, SC injections are more reliable response
• Oral absorption is slow and erratic
• It has linear pharmacokinetic profile allows more predictable and more flexible doses
Distribution

- Morphine enters all body tissues including the fetus of pregnant women, infants born to addicted mothers show withdrawal symptoms.
- Only small percentage of morphine crosses the BBB because it is a weak lipophilic, in contrast the more lipid-soluble opioids such as fentanyl readily penetrate into the CNS.
- The duration of action is 4 to 5 hours when administrated systemically to morphine-naïve individuals, longer when injected epidurally (low lipophilicity prevents redistribution).
Elimination

- It's conjugated with glucuronic acid in the liver to 2 main metabolites; morphine-6-glucuronide is a very potent analgesic + morphine-3-glucuronide doesn't have analgesic activity
- Excreted primarily in urine, small amounts in bile
• With age
  • Elderly patients consider low starting doses bcz. They are more sensitive to the analgesic effect; due to decrease metabolism, lean body mass or renal function.
  • Neonates shouldn’t receive morphine bcz. Of their low conjugated capacity.
Adverse effect

- HOTN
- DYS PHORIA anxiety and depression
- SEDATION
- CONSTIPATION
- URINARY RETENSION
- NAUSEA
- POTENTIAL FOR ADDICTION
- RESPIRATORY DEPRESSION
CONTRAINICATIONS

- Elevated ICP
- Respiratory depression
- Paralytic ileus or delayed gastric emptying
- Pregnancy and lactation
- In children

- USED WITH CAUTION
- Asthma, liver dz., renal dysfunction
Drug interactions

- **MAO inhibitors**, absolute contraindication due to high incidence of hyperpyrexia coma
- **Sedatives** increased CNS depression, particularly respiratory depression
- **Tricyclic antidepressant and antipsychotic agents** increased sedation. Variable effect on respiratory depression
Fentanyl

• Synthetic opioid has 100 fold the analgesic potency of morphine, it binds to M receptor 50 to 100 times more strongly than morphine, can also bind to D and K receptors

• The drug is highly lipophilic, rapid onset of action and short duration of action
• Onset IV 1-2 min   IM  8min
• Peak IV 3-5 min
• Duration IV 30-60 min   IM 1-2 HRS
DOSAGE

1. Adjunct to general anesthesia \ slow IV
   Low dose 0.5-2mcg/kg/dose
   Moderate dose ; initial 2-20mcg/kg/dose
     maintenance 1-2mcg/kg
   High dose 20-50mcg/kg
2. Pain management \ IV
   Bolus; 1-2mcg/kg
   Infusion ; 1-2mcg/kg/hr
Medical use

• IV is often used for anesthesia and analgesia
  • Anesthesia along with hypnotic agent like propofol
  • Sedation along with benzodiazepines (endoscopy or cath)

• Epidurally combined with local anesthetics (labor)
• Intrathecally as part of spinal anesthesia
• Oral transmucosal preparation (lozenges) used in treatment of cancer pt. with breakthrough pain who are tolerant to opioids

• The transdermal patch delayed onset (12 hrs) and prolonged offset, duration (48 to 73 hrs), used in chronic pain management, absorption depends on skin TEMP

• In children intranasal fentanyl is useful for treatment of mild to moderate pain
Adverse effects

• 1. bradycardia
• 2. confusion, dizziness
• 3. dehydration
• 4. constipation, nausea and vomiting, xerostomia
• 5. pain at the injection site
• 6. muscle rigidity
• 7. miosis
• 8. respiratory depression
• 9. diaphoresis
• Rare adverse effects
  • Abdominal pain, headache and fatigue
  • Anorexia and weight loss
  • Hallucinations
  • Urinary retention
  • Aphasia

• Fentanyl induce less nausea and histamine mediated itching in relation to morphine
• Fentanyl is metabolized to inactive metabolites by the CYP450 3A4 system
• Drugs that inhibit this isoenzyme can potentiate the effect of fentanyl as amiodarone
• Eliminated in the urine
Fentanyl and Morphine

**Fentanyl** is the most narcotic agent used during induction of anesthesia due to its rapid onset (highly lipid soluble) and predictable duration of action (30 minutes).

**Morphine** is used in the perioperative period to provide long lasting analgesia. And it should be administered slowly at a rate < 5 mg/min to avoid excessive histamine release.
Narcotic antagonist
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.
Given in small gradual 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 micg/kg/hour of naloxone is required.
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%)
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
Midazolam

- More potent than diazepam or lorazepam
- Induction slow, recovery prolonged
- May depress respirations when used with narcotics
- Minimal cardiac effects
- Water soluble
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<th>Agent</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>Cerebral</th>
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<td>HR</td>
<td>MAP</td>
<td>Vent</td>
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<tr>
<td>Barbiturates</td>
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<td>Thiopental</td>
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<td>Thiamylal</td>
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<td>Methohexital</td>
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<td>Ketamine</td>
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<td>Etomidate</td>
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<td>Propofol</td>
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<tr>
<td>Drug</td>
<td>Induction and Recovery</td>
<td>Main Unwanted Effects</td>
<td>Notes</td>
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<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>Psychotomimetic effects 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>
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