PHARMACOLOGY

LECTURE NO. 6

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General Anesthetics

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General Anesthetics

- **General anesthesia is typically a state of analgesia, amnesia, loss of consciousness, inhibition of sensory and autonomic reflexes, and skeletal muscle relaxation.**
- **This is achieved by a combination of intravenous and inhaled drugs.**

More than sleep

Skeletal muscle relaxation alone doesn't mean anesthesia. Muscle relaxants (mentioned in MSS) do not cause analgesia, amnesia, loss of consciousness.

Inhibition of reflexes such as bradycardia, laryngospasm, nausea, and vomiting during the operation to avoid aspiration to the airway and respiratory infection

Because there is no single drug that can cause all these effects.

General Anesthetics

Types of General Anesthesia:

A. Intravenous agents used alone, or in combination with other anesthetic agents (inhalation), to achieve an anesthetic state or sedation. These IV drugs include:

1. Barbiturates: Thiopental, methohexital.
2. Benzodiazepines: Midazolam, diazepam.
3. Propofol.

Usually IV agents are used first (for induction of anesthesia), followed by inhalational agents (for maintenance of anesthesia).

General Anesthetics

4. **Ketamine.**
5. **Opioid analgesics: Morphine, fentanyl, sufentanil, alfentanil, remifentanil.**
6. **Miscellaneous sedative-hypnotics: Etomidate, dexmedetomidine.**

↳ Must enter the body by lungs.

B. Inhaled anesthetics which include:

1. **Volatile liquids: Halothane, isoflurane, desflurane, enflurane, methoxyflurane, and sevoflurane.**
2. **Gases: Nitrous oxide.** Xenon gas is undergoing experiments to be used for anesthesia.

General Anesthetics

- **No anesthetic agent can produce the five desired effects without adverse effects.**
- **Balanced anesthesia employs multiple drugs (inhaled anesthetics, sedative-hypnotics, opioids, neuromuscular blocking drugs) to minimize unwanted effects.**

General Anesthetics

Although general anesthesia can be produced by only intravenous or only inhaled anesthetic agents, modern anesthesia typically involves a combination of:

1. **IV agents for induction of anesthesia.**
2. **Inhaled agents for maintenance of anesthesia.**
3. **Muscle relaxants.**
4. **Analgesics.**
5. **Cardiovascular drugs to control autonomic responses.** Premedications are used to reduce reflexes with adverse effects.

Intravenous Anesthetics

- **Are commonly used for induction of general anesthesia because of more rapid onset than inhaled agents. (immediate action)**
- **They are also used to provide sedation for patients in ICU settings.**
- **Rapid onset is due to their lipophilicity and preferentially partition into highly perfused lipophilic tissues (brain, spinal cord).**

→ Cross BBB.

Intravenous Anesthetics

- **Recovery is rapid and permits their use for short procedures.**
- **Termination of the effect of a single bolus is determined by redistribution of the drug into less perfused and inactive tissues such as skeletal muscle and fat, and is not related to their metabolism or renal excretion.**

IV anesthetics duration of action is approximately 10 minutes then the inhalational agents take over. In a 5 minutes operation IV agents are used alone without inhalational agents.

Propofol

- **It interacts with $GABA_A$ receptor-chloride channel. It also potentiate glycine-gated currents.**
- **Propofol acts as hypnotic but does not have analgesic properties.** Facilitates the activities of GABA and glycine.
- **It is the most popular IV anesthetic, and has replaced barbiturates.**
- **Its rate of onset of action is similar to IV barbiturates but recovery is more rapid and patient ambulation is earlier.** Patient ambulation: the ability of the patient to walk and return to normal activities postoperatively.
- **The patient subjectively feel better in the immediate postoperative period because of the reduction in postoperative nausea and vomiting.**

Propofol

- **It is the agent of choice for ambulatory surgery.**

Ambulatory (day case) surgery: surgery that does not require an overnight hospital stay.

- **It can be used for both induction and maintenance of anesthesia.**

If propofol is used for induction of anesthesia it is administered by a single IV injection, but for maintenance of anesthesia multiple infusions are used.

- **It reduces the required concentration of inhaled anesthetics.**

Propofol reduces the adverse effects of other anesthetic agents because it reduces the required doses of them.

- **When used during maintenance of anesthesia, propofol infusion (hypnotic) can be combined with IV opioids (analgesics) and neuromuscular blockers (muscle relaxants) to completely avoid the use of inhaled anesthetics.**

IV agents can be used alone if there is a contraindication for inhalational agents. Propofol is used among these agents for maintenance of anesthesia.

Propofol

When used for maintenance.

- It is effective in producing prolonged sedation (desirable) in patients in critical care setting, but cumulative effect can lead to delayed arousal. (undesirable)
- The recovery from propofol is more complete, with less “hangover” than that observed with thiopental.
- Prolonged administration of conventional emulsion formulation can raise serum lipids. (undesirable)

Conventional emulsions are used for the administration of lipid soluble drugs such as propofol, these emulsions are composed of fat, fatty acids, glycerol, etc.

Propofol

- **When used in critically ill young children for sedation, it has caused severe acidosis in the presence of respiratory infection and to possible neurologic sequelae upon withdrawal.**
- **It produces depression of central ventilatory drive and apnea.** (Which also causes acidosis)

Respiratory infection → hypoxia → accumulation of CO_2 → respiratory acidosis.

Propofol

- **Excitatory effects such as twitching or spontaneous movement are occasionally observed during induction of anesthesia.**
- **These effects can be confused with seizures.**
- **It produces a marked decrease in blood pressure during induction of anesthesia through arterial and veno dilation.**

Propofol

- **It has the greatest direct negative inotropic effect than other IV anesthetics.** → Reduce contractility of the heart.
- **Profound bradycardia and asystole have been reported.** → Atropine is used to prevent bradycardia → Stopping of contraction (fatal).
- **Pain at the site of injection is the most common adverse effect after IV bolus administration (reduced by admixture with local anesthetics such as lidocaine).**

Propofol

- **Muscle movements, hypotonus and rarely tremors have been reported after prolonged use.** undesirable
- **Propofol decreases cerebral blood flow, which decreases intracranial pressure (ICP) and intraocular pressure, but may lead to decrease in cerebral perfusion pressure.**

Beneficial only for a patient with elevated ICP

Fospropofol

- **Fospropofol is a water-soluble prodrug of propofol.**
- **The effects of fospropofol are similar to that of propofol, but onset and recovery are prolonged compared with propofol because the prodrug must first be converted into an active form.**
- **No injection site pain**
- **Can produce paresthesia in the perianal region.**

Etomidate

- It has hypnotic but no analgesic effects.
- It acts primarily through potentiation of $GABA_A$-mediated chloride current.
- It is used for induction of anesthesia in patients with limited cardiovascular reserve, because it causes minimal cardiovascular and respiratory depression and minimal hypotension.
- It produces rapid loss of consciousness.
- Recovery is less rapid than that of propofol.

Etomidate

- **Distribution of etomidate is rapid.**
- **Redistribution of the drug from the brain to highly perfused tissues is responsible for the short duration of action.**
- **It is a potent cerebral vasoconstrictor, leading to decreased cerebral blood flow and ICP, like thiopental.**

Etomidate

Adverse effects:

1. **Pain upon injection.** Same as propofol.
2. **Myoclonic activity.** Same as propofol.
3. **Postoperative nausea and vomiting.** More than propofol.
4. **It may activate seizure foci.** In patients with epilepsy.

Etomidate

The most important adverse effect which limits its long-term use:

5. **Inhibition of steroidogenesis (inhibition of 11β-hydroxylase) with decreased plasma levels of cortisol and hypoadrenalism → hypotension, electrolyte imbalance and oliguria.**

- **Not used as continuous infusion.**

  Only used by injection.

Ketamine

- **It produces a "dissociative anesthetic state" characterized by catatonia (muscular rigidity and mental stupor, sometimes alternating with great excitement and confusion, eyes remain open with a slow nystagmic gaze), amnesia and analgesia, with or without loss of consciousness.**

  Patient generally remains conscious but dissociates from the environment.

- **It is chemically related to phencyclidine, a psychoactive drug with high abuse potential.**

Extra: mental stupor is the lack of critical mental function and a level of consciousness.

Ketamine

Mechanism of Action:

- **It blocks glutamic acid NMDA receptor subtype.**

Pharmacokinetics:

- **It is highly lipid soluble and rapidly distributed into well-perfused organs, including brain, then it redistributes to less well perfused tissues.**

Ketamine

Pharmacodynamics:

- **It is the only IV anesthetic that have both analgesic properties and the ability to produce dose-related cardiovascular stimulation.**
- **It can be administered by multiple routes (intravenous, intramuscular, oral, rectal, epidural)**

Drug	Cardiovascular effect
Propofol, thiopental	Depression
Etomidate	Minimal effect
Ketamine	stimulation

Ketamine

- **It stimulates the central sympathetic nervous system and, to a lesser extent, inhibits the reuptake of norepinephrine at sympathetic nerve terminals.**
- **It increases heart rate, cardiac output and arterial blood pressure (transient).**

These effect are transient only if the drug is used as a single dose.

- **It increases cerebral blood flow, oxygen consumption, and intracranial pressure (ICP).**
- **It is dangerous in patients with elevated ICP.**

Not used for patients with head injury or tumors

Ketamine

- **It decreases respiratory rate but upper airway muscle tone is well maintained and airway reflexes are usually preserved.**
- **It relaxes bronchial smooth muscle.** Desirable

  ↳ Undesirable because it might cause aspiration.
- **Lacrimation and salivation are increased. This effect can be limited by premedication with an anticholinergic drug such as atropine.**
- **May cause laryngospasm especially in children.**

  ↳ A result of increased salivation..

Ketamine

- **Its use has been associated with postoperative disorientation, sensory and perceptual illusions, and vivid colorful dreams, out-of body experiences and increased and distorted visual, tactile, and auditory sensitivity. (This is called emergence phenomena).**
- **These reactions can be associated with fear and confusion**
  - **Disorientation**: related to place, person, and time. The patient doesn't recognize people around them, where they are, or what time is it.
  - **Vivid dreams**: dreams thought to be real.
  - **Out-of body experience**: a phenomenon in which a person perceives the world from a location outside their physical body

Ketamine

- **A euphoric state may be induced explaining the potential for its abuse.**
  - Emergence phenomena, fear, confusion, and euphoria.
- **These effects can be reduced by premedication with a benzodiazepine (diazepam, midazolam).**
- **It is specially useful in patients undergoing painful procedures such as burn dressing.**
- **It reduces opioid tolerance and opioid-induced hyperalgesia.**