### III. GENERAL ANESTHETICS

**General anesthetics** are pharmacologically active substances that suppress temporarily and reversibly the state of consciousness, sensitivity to pain, somatic, autonomic reflexes.

#### Classification of general anesthetics

- **1. Inhalational general anesthetics:**
  - gases: Nitrous oxide, Cyclopropane
  - volatile liquids: Halothane, Isoflurane, Enflurane, Desflurane, Sevoflurane, Methoxyflurane, Ethilic ether, Chloroform

- **2. Intravenous general anesthetics:**
  - Thiobarbiturates (very short acting barbiturates): Hexobarbital, Thiopental, Methohexital, Thiamilal, Thiobutabarbitral;
  - benzodiazepines (as adjuncts in anesthesia): Midazolam, Diazepam, Lorazepam;
  - imidazoles: Etomidate
  - steroid structure: Althesin
  - opioid analgesics: Morphine, Fentanyl, Sufentanil, Alfentanil, Remifentanil
  - others: Propofol, Ketamine, Dexmedetomidine, Propanidid.

#### Preanesthetic medication

- cholinoreceptor-bloking drugs (anticholinergic drugs) → reduce salivary and bronchial secretion, prevent vagal bradycardia and reflex hypotension.
- antihistaminic drugs → antialergic and antiemetic effects, 1st generation has also sedative effects
- benzodiazepines → anxiolytic-sedative-hypnotic effects
- opioids are analgesic drugs that potentiate analgesic effect of general anesthetics
- neuroleptic drugs
- antiplatelet drugs: Abciximab, Eptifibatide → prevent venous thrombosis.

**A good general anesthesia is characterized by:**

- good muscle relaxation.
- the depth of general anesthesia is continuously monitored at all time frames.
- installation and recovery of anesthesia must be quick, with fewer adverse effects.
- the general anesthetic should have a high index narcotic.

#### Stages of general anesthesia using a single general anesthetic:

- **1. Stage of analgesia:**
  - depression of certain cortical and spinal cord areas, of spinothalamic tract;
  - initially analgesia without amnesia (state of consciousness is maintained), later are produced both analgesia and amnesia;

- **2. Stage of excitement:**
  - depression of small inhibitory circuits and amnesia (no consciousness);
  - hyperexcitability (delirium, excitation, vomiting, irregular respirations);

- **3. Stage of Surgical Anesthesia:**
  - depression of ascending reticular activation system (but with the maintenance of the sensitivity of bulbar vegetative centers) and skeletal muscle relaxation;
• Four stages represent the increasing depth of anesthesia:
  o changes in ocular movements,
  o reduced eye reflexes,
  o changes in pupil size,
  o respiratory depression.

➤ 4. Stage of Medullary Depression
• toxic paralysis of bulbar centers (severe depression of the vasomotor and respiratory center) → death rapidly ensues.

Recovery from general anesthesia follows the same stages, in reversed order.

Depth of anesthesia is dependent upon the concentration of anesthetic in the CNS, the lipophilicity of the general anesthetic and the reactivity of the patient. Achievement of an adequate brain concentration of an inhaled anesthetic requires transfer of that anesthetic from the alveolar air to blood and then to brain. The transfer of an anesthetic from the lungs to the arterial blood depends on its solubility, evaluated by the blood:gas partition coefficient (the relative affinity of an anesthetic for the blood compared to air). There is an inverse relationship between the blood solubility of an anesthetic and the onset of action. Eg, nitrous oxide has low solubility in blood (low blood:gas partition coefficient), so, little of the anesthetic dissolves in the blood, which in turn results in rapid equilibration between the inhaled anesthetic and arterial blood, respectively rapid equilibration with the brain and fast onset of action.

**Potency of an inhalational anesthetic agent** depends on the minimum alveolar concentration (MAC), with 1 MAC defined as the minimum alveolar concentration that results in immobility (loss of response) in 50% of patients in response to surgical incision. MAC is usually expressed as the percentage of gas in a mixture required to achieve the effect (MAC is small for potent anesthetics).

**Potency of an intravenous anesthetic agent** depends on the free plasma drug concentration that results in immobility (loss of response) to surgical incision in 50% of subjects.

1. INHALATIONAL GENERAL ANESTHETICS
1.1. GASES

➤ **Nitrous Oxide** (*N₂O*) (“laughing gas”)
• It is a gas, non-explosive, colorless, odorless, tasteless. The blood:gas partition coefficient is low. It is a potent analgesic, but it has a very low narcotic effect.

**Indications:**
• general anesthesia (only in association with general anesthetics volatile liquids);
• analgesia in obstetrics (for labor).

**Adverse reactions:**
• sensitivity to cathecolamines, depression of the myocardium;
• increase in cerebral perfusion and increase in intracranial pressure.

**Contraindications:**
• pneumothorax;
• pneumopericardium;
• renal cysts, lung cysts;
• bowel obstruction (= intestinal occlusion);
• first two trimesters of pregnancy (because of its effects on DNA production).
1.2. VOLATILE LIQUIDS
These drugs have a high narcotic effect, but low analgesic effect.

**Mechanisms of action:**
- reduce time of opening of Ach-dependent Na+ channels;
- agonists on GABA-A receptors;
- agonists on α2 presynaptic receptors; activate K+ channels and block Ca2+ channels associated with α2 presynaptic receptors.

**Pharmacokinetics:** metabolism in the liver: Halothane >40%, Isoflurane <2%, Enflurane = 8%, Desflurane = 0.05%, Sevoflurane = 2-5%, Methoxyflurane >70%.

**Indications:** induction or maintenance of general anesthesia

**Adverse reactions:**
- **HALOTHANE**
  - hepatotoxicity (hepatic failure appears to be greatly increased by repeated exposure to halothane; toxicity to halothane is rare and not severe in children)
  - high cardiac sensitivity to catecholamines, resulting in an increased incidence of cardiac arrhythmias due to myocardial excitability;
  - depression of the myocardium (this drug does not allow compensatory sympathetic response) → reduce cardiac output and hypotension;
  - respiratory depression;
  - increase intracranial pressure.
- **ISOFLURANE, ENFLURANE, SEVOFLURANE**
  - moderate sensitivity to catecholamines;
  - decrease blood pressure and determine a compensatory tachycardia → these drugs are contraindicated in coronary artery disease.
- **METHOXIFLURANE**
  - hepatotoxicity
  - high cardiac sensibility to catecholamines
- **ETHYL ETHER** (is flammable in contact with oxygen or air; irritates the respiratory tract → stimulates bronchial secretion, salivation, coughing, laryngeal spasm; nausea and vomiting; increase levels of circulating catecholamines).

2. INTRAVENOUS GENERAL ANESTHETICS
These drugs have a very high narcotic effects, but with very low/absent analgesic effects.

**Indications:** induction or maintenance of general anesthesia.

- **THIOBARBITURATES** (narcotics barbiturates) see Chapter Sedative-hypnotic drugs.
  - determines narcotic sleep in a few seconds, duration of 10-20 minutes;
- **PROPOFOL (2,6-DIISOPROPYLPHENOL)** is similar to barbiturates narcotics.
  - determines narcotic sleep in 40 seconds;
  - is widely used because it produces an euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting.
  - indications: induction or maintenance of general anesthesia.
- **ETOMIDATE** is a derivative of imidazole
  - determines narcotic sleep in a few seconds, a duration of 7-14 minutes;
  - metabolism in the liver and plasma (esterases);
  - indications: induction of general anesthesia in patients with coronary artery disease or cardiovascular dysfunction (because don’t influence heart activity).
  - Disadvantages: pain at the site of injection, myoclonus; rarely: apnea.
PROPANIDID:
- very short duration of action (2-5 min); metabolism: by plasma pseudo-cholinesterases → increase the duration of action of succinylcholine; side effects: vasodilation, decrease blood pressure, negative inotropic effect, hyperventilation, apnea, phlebitis, allergy, vomiting, tonic-clonic seizures, death.

ALTHESIN\(^9\) (has steroid structure, but does not determine endocrine adverse effects).

BENZODIAZEPINES (DIAZEPAM, MIDAZOLAM, LORAZEPAM).

DISSOCIATIVE ANESTHESIA (realised with Ketamine)
Characteristics of dissociative anesthesia: catalepsy (immobility), amnesia and low visceral analgesia (“the patient feels dissociated from the environment”). Latency = few seconds (iv administration) or minutes (im administration); duration of action=12-25 min.

Mechanisms of action of KETAMINE:
- allosteric antagonist of the NMDA glutamate receptors;
- inhibit the reuptake of norepinephrine and dopamine.

Indications:
- pediatric surgery;
- induction of general anesthesia;
- orthopedic maneuvers;
- laryngoscopy;
- transport of patients from the accident site;
- burn wound dressing in adult patients.

Adverse effects: psychomotor agitation, hallucinations, the stupor, disorders of consciousness, adiction and effects of sympathetic stimulation.

Contraindications:
- patients with cardiovascular disease;
- neurosurgery (due to intracranial hypertension syndrome);
- ophthalmic surgery;
- pregnancy.

Disadvantage: Ketamine does not produce skeletal muscle relaxation and does not influence pharyngeal and laryngeal reflexes.

NEUROLEPTANALGESIA (Fentanyl combined with Droperidol/Haloperidol)
The characteristics of neuroleptanalgesia: preserve consciousness, the patient answers to questions (useful in surgery of the inner ear, thyroid, neurosurgery; insensitivity to pain is achieved with fentanyl, complete disinterest is achieved with droperidol (neuroleptic).

Indications:
- preoperative preparation;
- endoscopies; neuro-radiological explorations;
- potentiation of regional anesthesia;
- burn wound dressing in adult patients;
- cardiac surgery; elderly;
- neurosurgery (neuroleptanalgesia not determine the syndrome of intracranial hypertension); surgery of the inner ear; thyroid surgery.

Neuroleptanesthesia = neuroleptanalgesia + nitrous oxide + skeletal muscle relaxant.

It is now withdrawn from the market of different countries due to severe drug reactions.

Lecturer Cristina GHICIUC, MD, PhD