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General anesthetics

Department of Pharmacology MU

General anesthesia (GA)

General anesthesia is an induced short-term fully **reversible** deep unconsciousness combined with analgesia while perception of pain is eliminated and muscles are relaxed.

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History

- October 1846 in Massachusetts General Hospital in Boston, USA – the first public demonstration of ether GA
- dentist William Thomas Green Morton
- patient: Edward Gilbert Abbott, 22 years old, neck tumor

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https://commons.wikimedia.org/wiki/File:Roots-criticall-care.jpeg

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Stages of GA are historically characterized by Guedel's scheme

- following use of ether (today historical and didactical meaning only)

No anesthesia runs according to this scheme presently.

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General anesthetics

- **Inhalational**

  liquid

  gaseous

- **Intravenous**

  barbiturates

  non-barbiturates

  benzodiazepines

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Inhalational anesthetics
Physical and Chemical Properties

- gases
- liquids

  (fluid under normal pressure - boiling point about 50°C, a special device is necessary for their use - vaporizer)

- concentration of general anesthetic in the CNS depends on its concentration in blood and this correlates with its concentration in the inhaled air

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Inhalational anesthetics

Mechanism of action:

- dependent on liposolubility of the drugs (anesthetic effect of inhalational anesthetics grows with increasing liposolubility) – so called lipid (biophysical theory);

  Overton–Meyer's correlation: anesthetic potency is closely associated with liposulubility, not with chemical structure

- non-specific influence on ion channels in neuronal membranes

MAC – minimal alveolar concentration = concentation which induces stadium of tolerance in 50 % of patients

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Liquid (volatile) inhalational anesthetics

isoflurane

- low metabolisation
- increases effect of muscle relaxants, causes hypotension
- pungent smell – disadvantage in pediatrics

desflurane

- fast onset and recovery, pungent smell
- used only for maintenance of anesthesia
- suitable in obese patients (bariatric surgery) and in 1-day surgery

sevoflurane

- fast onset and recovery
- pleasant fruit smell
- most widely used in pediatrics

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Extent of metabolization

Inhalational anesthetic drug	Conversion to metabolites
desflurane	0,2 %
isoflurane	0,2 %
sevoflurane	3 %
halothane (obsolete)	15-20 %
methoxyflurane (obsolete)	50 %

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Liquid (volatile) inhalational anesthetics

HISTORY

diethylether (ether) used exceptionally nowadays (explosive, long excitatory stage, irritation of mucous membranes)

advantage – low boiling point – can be used without anesthetic machine under field conditions

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Gaseous inhalational anesthetics

nitrous oxide N_2O (laughing gas)

- MA: inhibition of NMDA receptor
- low anesthetic potency, effective analgesic drug
- rapid onset and recovery, used in combined anesthesia (in obstetrics as monotherapy) and with muscle relaxants

AE:

- supraventricular arrhythmia
- hallucinations, potentiates postoperative nausea

  risk of bone marrow suppression following exposition > 6 h. -

  (megaloblastic anemia, agranulocytosis following chronic use)
- not to be used in conditions with presence of gas in cavities (pneumothorax - risk of increase in intrathoracic press shift of mediastinum)

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Intravenous general anesthetics

1. **BARBITURATES**
2. **NON-BARBITURATES**
3. **BENZODIAZEPINES**

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1. BARBITURATES

thiopental

- MA: increases inhibitory effect of GABA receptor
- for induction to anesthesia
- fast onset (20s), duration 5-10 min
- redistribution from the brain to muscles and fat – need of higher dose in obese patients, slow recovery in obese patients, „hang over“ during recovery
- accidental injection into an artery causes pain and even necrosis or gangrene

KI: in patients with liver damage, porphyria

AE: cardiovascular and respiratory depression, vasodilation, negative inotropic effect; immunosuppression (following long-term use)

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2. NON-BARBITURATES

ketamine

- for induction or maintenance of short-term surgical procedures, it causes strong analgesia
- MA: inhibition of NMDA receptor
- patients experience dissociation from the environment and self → **dissociative anesthesia**
- onset 1-2 min. following i.v. administration
- suitable in pediatrics, in patients with hypovolemic shock after injury; to decrease pain during small surgical procedures, in burns, for anesthesia during natural disasters and wars

AE: ↑ **blood pressure and pulse (it can be used in shock)**

after recovery living hallucinations (prevention: combination with benzodiazepines)

KI: hypertension, heart insufficiency, arteriosclerosis, intracranial hypertension, glaucoma

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propofol

- MA: increases activity of $GABA_A$ receptor
- for induction and maintenance of GA, it has no analgesic effects, fast onset (30 s), short duration (t ½ 2-4 min)
- administered as emulsion oil in water, which causes pain and increases risk of bacterial propagation in vial
- prodrug fospropofol (soluble in water, Lusedra in USA)
- AE: cardiovascular and respiratory depression, lactate acidosis

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Long-term use (higher doses) can cause „propofol syndrome“ - green coloration of urine and hair

http://www.doctoryg.com/2016/11/propofol-infusion-syndrome.html

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etomidate

- MA: allosterically increases affinity to GABA receptor
- for induction to GA, it has no analgesic effects
- fast onset, fast recovery, smaller risk of respiratory arrest
- for short-term surgical procedures: cardioversion

AE: myoclonus, tremor

↑ blood pressure, postoperative nausea and vomiting, pain during administration

not to be used in patients with suprarenal insufficiency, immunosuppression

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dexmedetomidine

- has analgesic and anesthetic/analgesic sparing effects
- for premedication and vegetative stabilization during surgery
- MA: specific agonist of α_2-adrenergic receptor
- highly soluble in fat (fast penetration to the CNS and fast onset of sedative and hemodynamic effects)

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dexmedetomidine (cont.)

- effect on presynaptic α_2-adrenergic receptors inhibits particularly release of noradrenaline, and furthermore acetylcholine, serotonin, dopamine and substance P

- use: in intensive care and for sedation

- AE: hypotension, bradycardia

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3. BENZODIAZEPINES

- their effect is caused by sensibilisation of binding site for GABA on chloride channel

midazolam

- for premedication, induction to GA
- depressive effect on respiration

- see topic Hypnosedatives

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Course of general anesthesia

1. Premedication
2. Induction
3. Maintenance
4. Recovery

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Premedication

- used to sedate and tranquillize the patient
- prevention of adverse effects (both of anestetic drugs and organism)
- decrease in consumption of anesthetics
- analgesia before the surgery
- ensuring amnesia
- decrease in gastric volume and acidity, prevention of aspiration pneumonia
- attenuation of vagal reflexes during intubation

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Class of drug	**Drug**	**Expected effect**
benzodiazepines	diazepam bromazepam midazolam	anxiolytic
antisecretoric agents, antacids	H_2 antihistamines (ranitidine, famotidine)	decrease in acidity of stomach content
opioids	fentanyl, sufentanil	analgesic
neuroleptic drugs	thioridazine, droperidol	central sedation + antiemetic effect

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Induction to GA

- shortly acting injection
  administration i.v. or i.m., rarely in children per rectum
  thiopental
  ketamine
  propofol
  (etomidate)

- for intubation muscle relaxation is necessary (depolarizing muscle relaxants)
  suxamethonium (onset of effects within 30 s, duration up to 3 min.)

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Maintenance of GA

- **Inhalational (balanced)**
  - combination of inhalational anesthetic drug, opioids and relaxants
  - mixture N_2O + O_2 (2:1) + sevoflurane or isoflurane + analgesic drugs + muscle relaxants

- **TIVA**
  - total i.v. anesthesia

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TIVA

- Bristol regime ("manual" infusion)
- premedication: benzodiazepine (temazepam)
- induction: fentanyl 2 μg/kg, bolus of propofol 1 mg/kg
- propofol infusion in scheme 10-8-6: 10 mg/kg/hour for 10 minutes, 8 mg/kg/hour for 10 minutes, 6 mg/kg/hour as needed
- patient on artificial ventilation
- advantage: decrease in propofol consumption, highe hemodynamic stability, faster recovery

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Recovery
anesthesia should subside spontaneously

When problems with recovery occur:

- neostigmine – blocks effects of non-depolarizing muscle relaxants (after surgery to terminate muscle relaxation)
- naloxone – restores vigility supports respiratory center (opioid antagonist)
- flumazenil – restores vigility (benzodiazepine antagonist)
- itopride, metoclopramide- prevention of postoperative nausea

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Recovery

- furosemide - in case of anuria
- noradrenaline - in case of hypotension
- beta-blockers (metoprolol) - in case of tachycardia
- sugammadex
  - coats molecules of peripheral (non-depolarizing) muscle relaxants and complexes are then eliminated by kidney
  - for fast decurarization
  - sugammadex has the largest effect on rocuronium, smaller on vecuronium and the smallest on pancuronium
- postoperative analgesia: morphine, piritramid, paracetamol, metamizole

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ALTERNATIVES OF GA

Neuroleptanalgesia

- neuroleptic drug + opioid analgesic drug

= state of psychomotor sedation, neurovegetative stability and analgesia

- amnesia after recovery, patient is not unconsciousness – important during neurosurgical procedures

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ALTERNATIVES OF GA

Analgosedation

- opioid analgesic drug + benzodiazepine
  midazolam (diazepam) + fentanyl

Tranquanalgesia

- i.v. anesthetic drug + benzodiazepine
  ketamine + midazolam (diazepam)

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Malignant hyperthermia

- disorder that can be considered a gene-environment interaction, it causes an increased release of calcium or limited re-uptake of calcium to sarcoplasmic reticulum in muscle cells

- the most common triggering agents are volatile anesthetics, (most frequently halothane) or the muscle relaxant suxamethonium

- symptoms: very high temperature, increased heart rate and abnormally rapid breathing, increased carbon dioxide production, increased oxygen consumption, mixed acidosis, rigid muscles, and rhabdomyolysis

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Malignant hyperthermia

- When suspect: discontinuation of triggering agents, and supportive therapy directed at correcting hyperthermia, acidosis, and organ dysfunction
- treatment is the intravenous administration of **dantrolene**, the only known antidote
- testing: a muscle (small part of musculus femoralis) biopsy is carried out
- National center for malignant hyperthermia was founded in Brno in 2001

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Most frequent complication of GA

Induction

hypotension, dysrhythmia, laryngospasms, aspiration

Maintenance

hypo- and hypertension, dysrhythmia, hypoxia, hypothermia

Recovery

hypotension, tremor, delayed recovery, persisting muscle relaxation

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New substances

xenon (inhalational anesthetic drug – gas)

- the fastest introduction and recovery
- MA: inhibition of NMDA receptors
- non-toxic, no metabolisation, analgesic effect
- anti-apoptotic and neuroprotective effects

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