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Local anesthetics

Local anesthetics (LA)

- cause temporary loss of sensation in a limited area by local reversible inhibition of sensory neurons

- sensitivity of nerve fibers to LA:
  vegetative > sensory > motoric nerve fibers

- in sensory fibers the perception of heat is blocked first, later the perception of pain stimuli, and then also the touch

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LA - mechanism of action

- penetration into sensitive nerve fibers
- blockade of voltage-gated sodium channels responsible for fast depolarization along nerves
- binding on the inner side of the nerve membrane, and preventing Na^+ ions flow

other effects:

- vasodilation (sympathetic nerve fibers blockade)
- antiarrhythmic/proarrhythmic effects (influence on Na^+ channels in myocardium)

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LA - chemical structure

- amphiphilic substances:
  - aromatic group is lipophilic
  - nitrogen group is hydrophilic (ionisable)

connected via **ester** or **amide** bond (ester-type and amide-type)

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LA - chemical structure

- LA are weak bases

  pKa = 8-9, efficacy of LA depends on tissue pH
  – ratio of ionized/non-ionized form

- higher pH = increased efficacy– more molecules are non-ionized = increased penetration to nerve fibers

- low pH = less effective, ionized molecules of LA do not penetrate to neurons, e.g. in tissues with inflammation

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LA - pharmacokinetics

- **absorption** depends on drug concentration on the site of administration, dose, blood perfusion, physical-chemical properties of drug and on the presence of vasoconstrictor agents

- **distribution**

- in the whole body, amides: strong binding to plasma proteins

- **metabolisation**

- plasmatic esterases are involved - fast (ester LA)
- hepatic metabolism via CYP- slower (amide LA)

- **excretion** of metabolites - kidneys

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Vasoconstrictor agents

- additives for lowering systemic toxicity
- compensation of vasodilation induced by LA
- decrease in LA consumption
- increased duration of analgesia (delayed diffusion of LA)

in acral parts with caution – risk of ischemic necrosis

adrenaline, ev. **noradrenaline**

alfa1-agonists (nafazolin)

derivatives of vasopressin

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LA – routes of administration

- **topical (surface)** anesthesia - transdermal penetration of LA in the form of solution, spray, gel, ointment

mucosa, cornea, esophagus, respiratory tract, decubitus

- frequently used in urology (catheterization) and before other painful instrumental procedures, inhalation of trimecaine before bronchoscopy

EMLA (eutectic mixture of local anesthetics) – mixture of lidocaine and prilocaine for topical use on intact skin.

EMLA is frequently used in pediatrics approximately 15-60 minutes before invasive procedure (blood collection, cannulation).

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LA – routes of administration

- **infiltration anesthesia**

  subcutaneous, submucosal, intramuscular, intraarticular

blocks nerve conduction near their site of administration

- low concentrations of both LA and vasoconstrictor agents

- often used for minor surgical and dental procedures

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LA – routes of administration

conduction anesthesia

- **peripheral** – block of both nerve trunks and individual nerves

- **central** – always without vasoconstrictor agents!

epidural anesthesia – perioperative and obstetric analgesia – it is necessary to stop in advance use of warfarin (+ anticoagulant agents), ASA (+ antiplatelet agents), LMWH, usual amount of LA 16 mL

subarachnoideal anesthesia (spinal, lumbal) – intrathecal administration of LA into intervertebral space, usual amount of LA 4 mL

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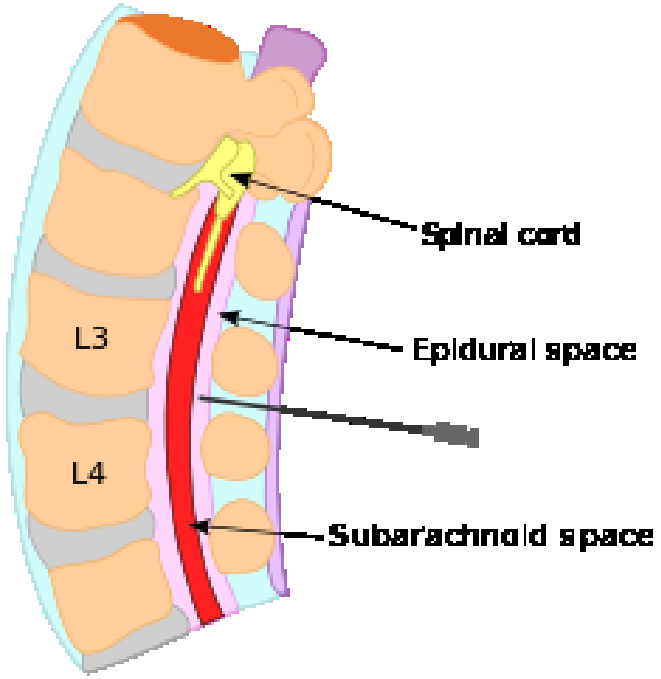

https://upload.wikimedia.org/wikipedia/commons/thumb/b/ba/Epidural_blood_patch.svg/250px-Epidural_blood_patch.svg.png

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LA – routes of administration

- **intravenous regional anesthesia (Bier block)**

- trimecaine 1%, lidocaine 0,5 %

- toxic LA should not be used (bupivacaine)

- quick onset and inhibition of motor functions

- exsanguination of the limb (elevation + tourniquets), procedures max. up to 2 hrs (risk of ischemia)

- no postoperative analgesia

- bleeding must be stopped carefully

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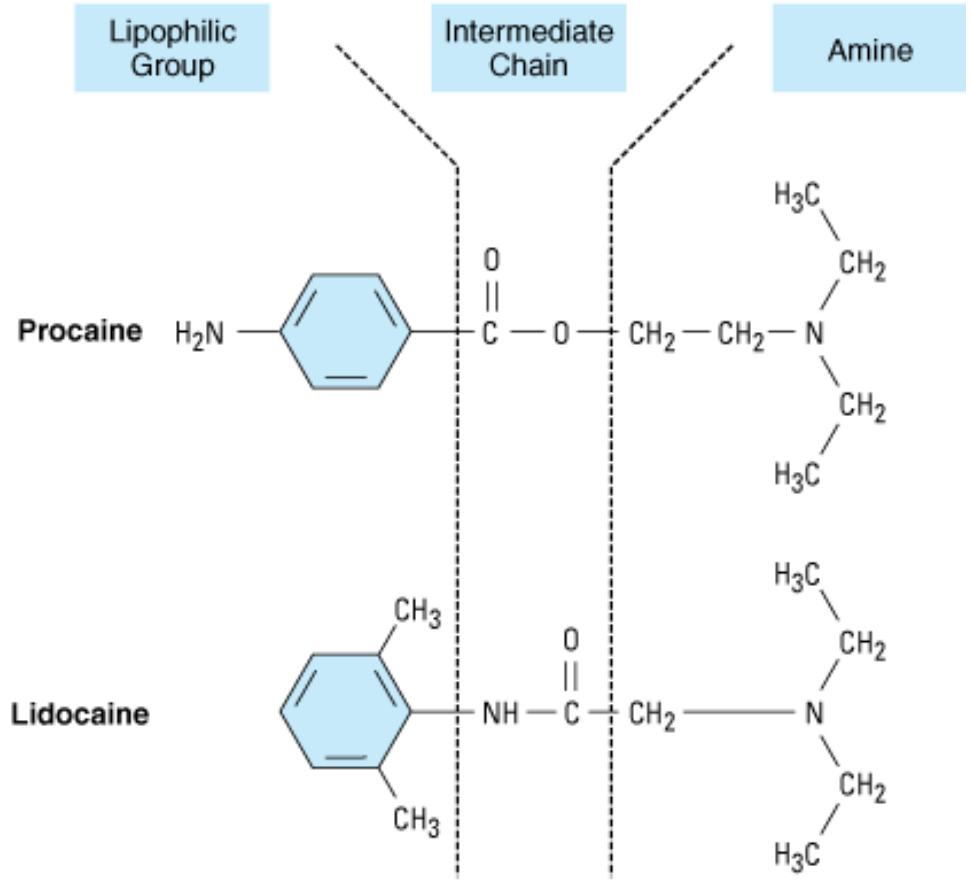

https://dentistryandmedicine.blogspot.cz/2012/05/regional-anesthesia-manualupper.html

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Ester type of LA

cocaine

- the first known LA (in use since 1884)
- natural compound, isolated from leaves of Erythroxylon coca
- central psychostimulant with high risk of addiction
- for surface anesthesia

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Ester type of LA

procaine

- the oldest synthetic LA (1905)
- slow onset, short duration
- for infiltration and conduction anesthesia (it penetrates poorly the skin)

tetracaine

- fast onset
- high systemic toxicity – only for surface anesthesia of oral cavity and throat (combined with chlorhexidine)

benzocaine

- only for topical anesthesia of oral cavity, ear and throat (available in combination with antiseptics)

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Ester type of LA

LA of ester type are structurally similar to para-aminobenzoic acid

→ high allergenic potential

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Amide type of LA

trimecaine

- universal, for all types of local anesthesia
- used also as the class I antiarrhythmic drug

lidocaine (syn. xylocaine and lignocaine)

- universal LA for surface, infiltration and conduction anesthesia
- class I antiarrhythmic drug

in patents treated with betalytics, $Ca2^{+}$ channel blockers and in patients with epilepsy doses of trimecaine and lidocaine must be halved

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Amide type of LA

mepivacaine

- in dentistry, in patients with KI of catecholamines

articaine

- used in dentistry
- fast onset, long effect

bupivacaine

- all type of local anesthesia
- treatment of acute pain - continually to epidural space
- cardiotoxic

levobupivacaine

- lower cardiovascular toxicity and neurotoxicity

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Amide type of LA

ropivacaine

- for all types of anesthesia except from subarachnoidal

prilocaine

- surface anesthesia EMLA
- spinal anesthesia for short surgical procedures

cinchocaine (dibucaine)

- surface (topical) anesthesia
- highly toxic

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Amide type of LA

Allergic reactions are less frequent

→ LA of amide type are used more frequently than LA of ester type

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LA - according to their efficacy

- weak
  procaine (effect lasts approximately 45 minutes),
  benzocaine

- intermediate
  trimecaine, lidocaine (effect lasts approximately 90 minutes)

- strong
  tetracaine, articaine, bupivacaine (effect lasts approximately 120 minutes-12 hours),
  levobupivacaine, ropivacaine, mepivacaine

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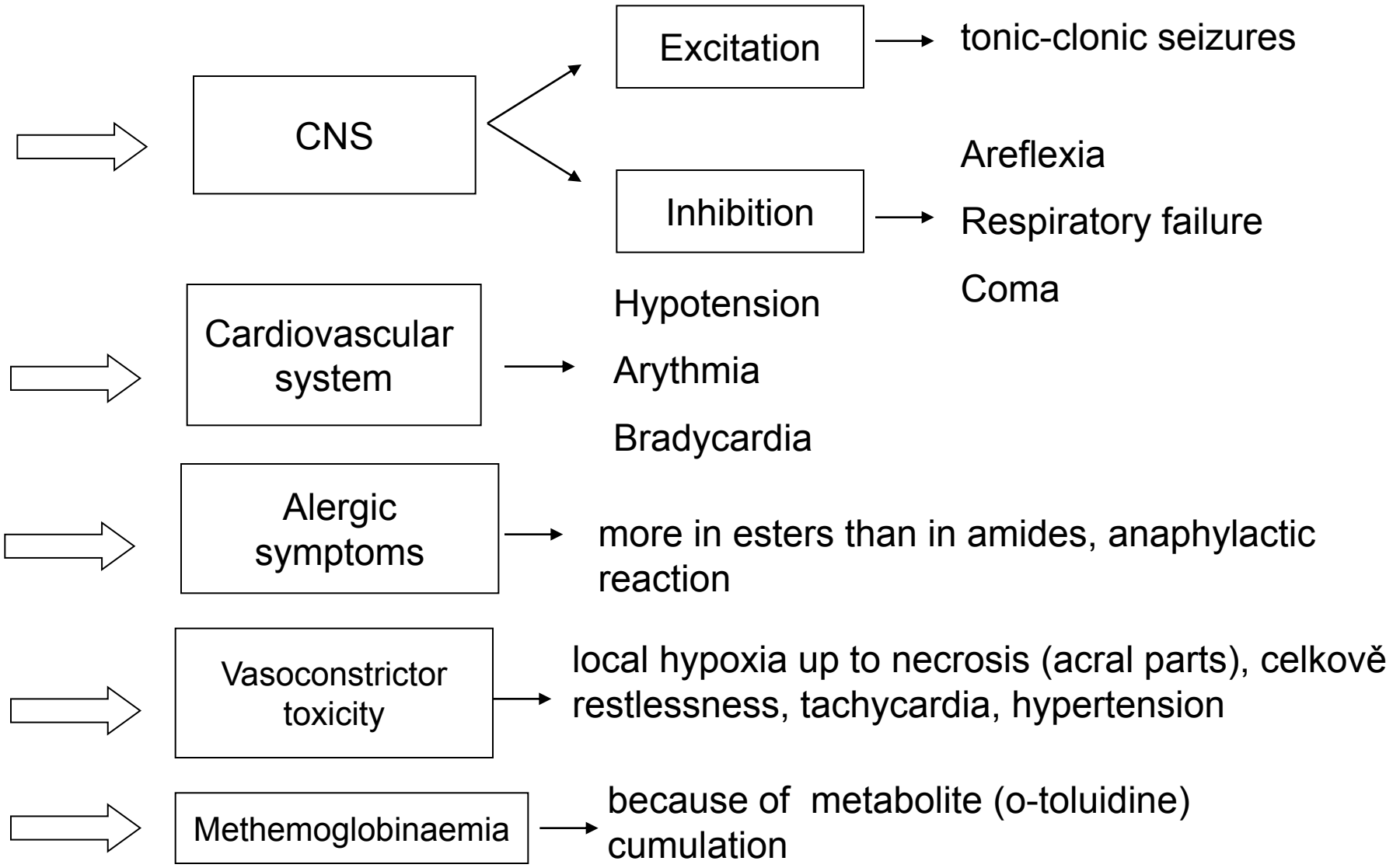
Toxic effects of LA



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Alergic and anaphylactic reaction to LA

symptoms:

- pruritus
- urticaria
- swellings
- anaphylactic shock- restlessness, anxiety, breathlessness, vomiting
- Quincke‘s oedema – without inflammation, fast onset in face, affecting lips, face and throat (suffocation!!)

therapy:

- oxygen and infusion of 5% substituive solution with noradrenaline
- hydrocortisone i.v.
- antihistamines
- in case of respiratory failure, keep free airways, artificial respiratory ventilation

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Systemic toxic reaction to LA

symptoms: (most often till 15 min from LA administration):
- restlessness, hand tingling, hot or cold, nausea, vertigo, cold sweat
- tachypnea
- tremor, fasciculations, seizures
- tachycardia, increased blood pressure in the beginning with the subsequent decrease, unconsciousness, bradycardia
- in the final phase respiratory and cardivascular failure

therapy:
- lay down patient, oxygen in respiratory insufficiency
- diazepam i.v. in seizures
- slow adrenaline continually i.v. if there is critical decrease of BP
- resuscitation in respiratory and cardiac failure

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Some of the LA can be also used as antiarrhythmic agents (class 1b).

lidocaine

trimecaine

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General anesthetics

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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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 pressure with 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, higher 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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