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

Sensitive nerve system

- signals from skin receptors and from skeletal muscles and joints, etc.

- protopathic perception - sensing pain, pressure, heat, or cold in a nonspecific manner

- epicritic perception - permits the discrimination and the topographic localization of the finer degrees of touch and temperature stimuli and proprioception (sense of the movements and position of the body independent of vision)

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)

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)

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

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

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

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).

LA – routes of administration

- **infiltration anesthesia**

  subcutaneous, submucosal, intramuscular, submucosal, 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

LA – routes of administration

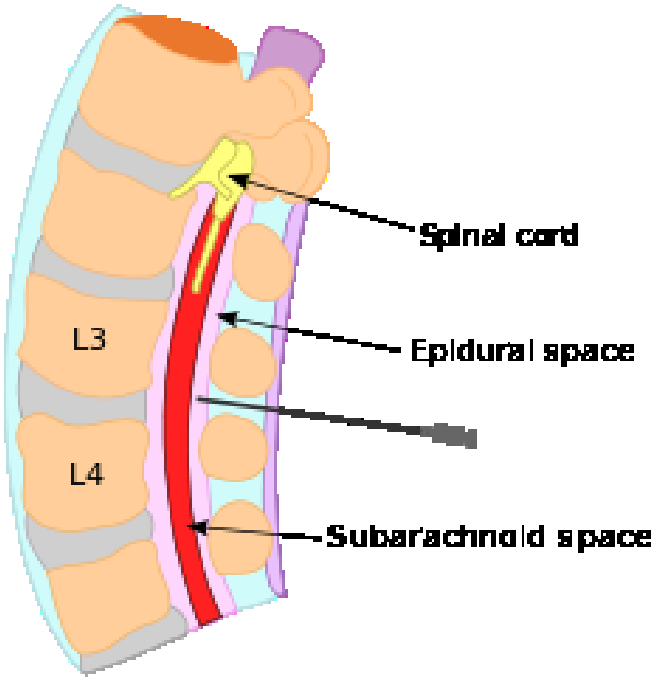
- **conduction anesthesia**

- **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



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

LA – routes of administration

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

- trimecaine 1%, lidocaine 0,5 %

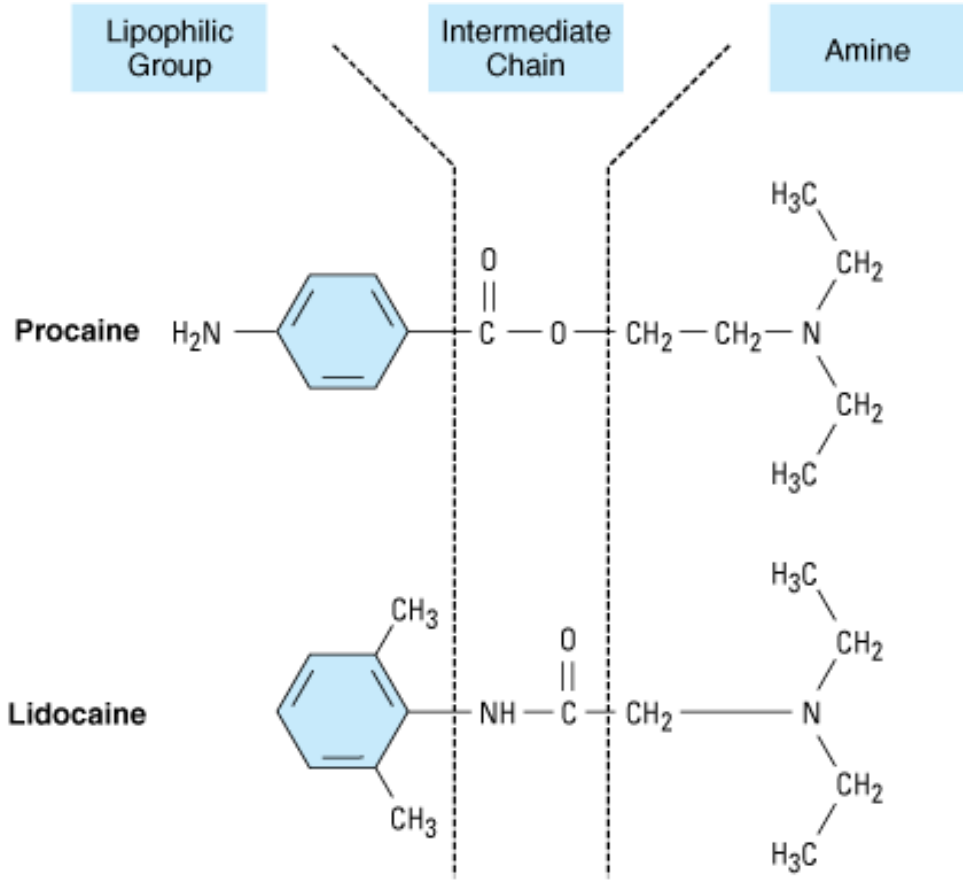
- toxic LA should not be used (bupivacaine)

- 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



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

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

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)

Ester type of LA

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

→ high allergenic potential

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

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

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

Amide type of LA

Allergic reactions are less frequent

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

LA - according to their efficacy

- weak

  procaine (effect lasts approximately 45 minutes), benzocaine

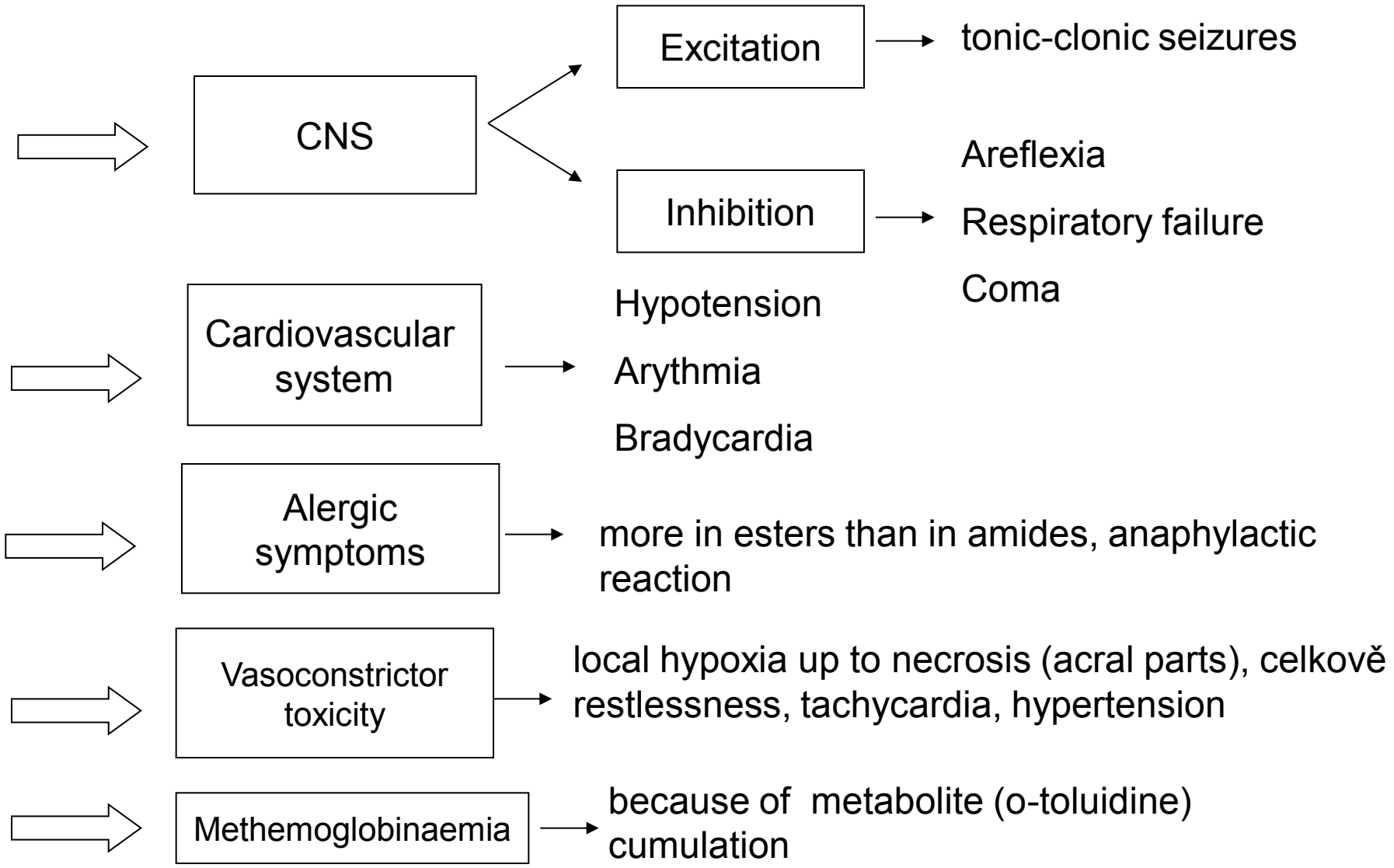
- intermediate

  trimecaine, lidocaine (effect lasts approximately 90 minutes)

- strong

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

Toxic effects of LA



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

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

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

lidocaine

trimecaine