



# 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

# 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  $\text{Na}^+$  ions flow

other effects:

- vasodilation (sympathetic nerve fibers blockade)
- antiarrhythmic/proarrhythmic effects (influence on  $\text{Na}^+$  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, 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

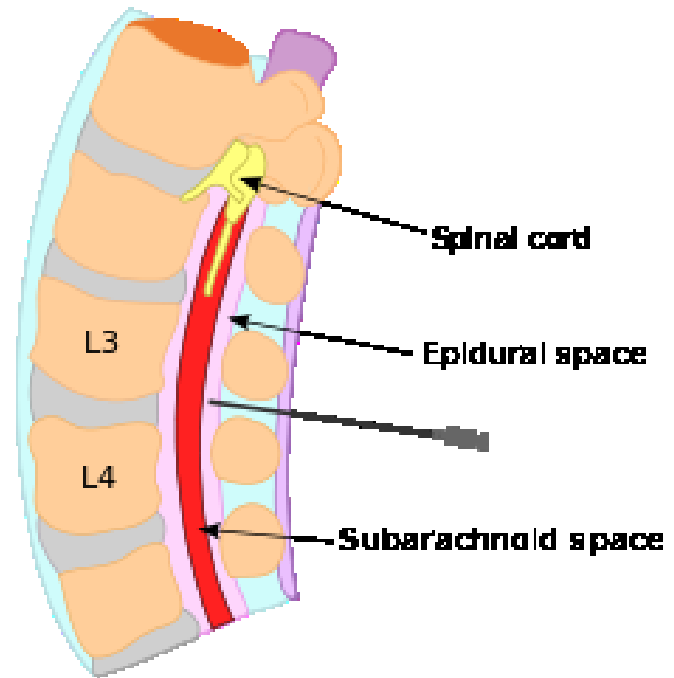


## □ conduction anesthesia

- **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

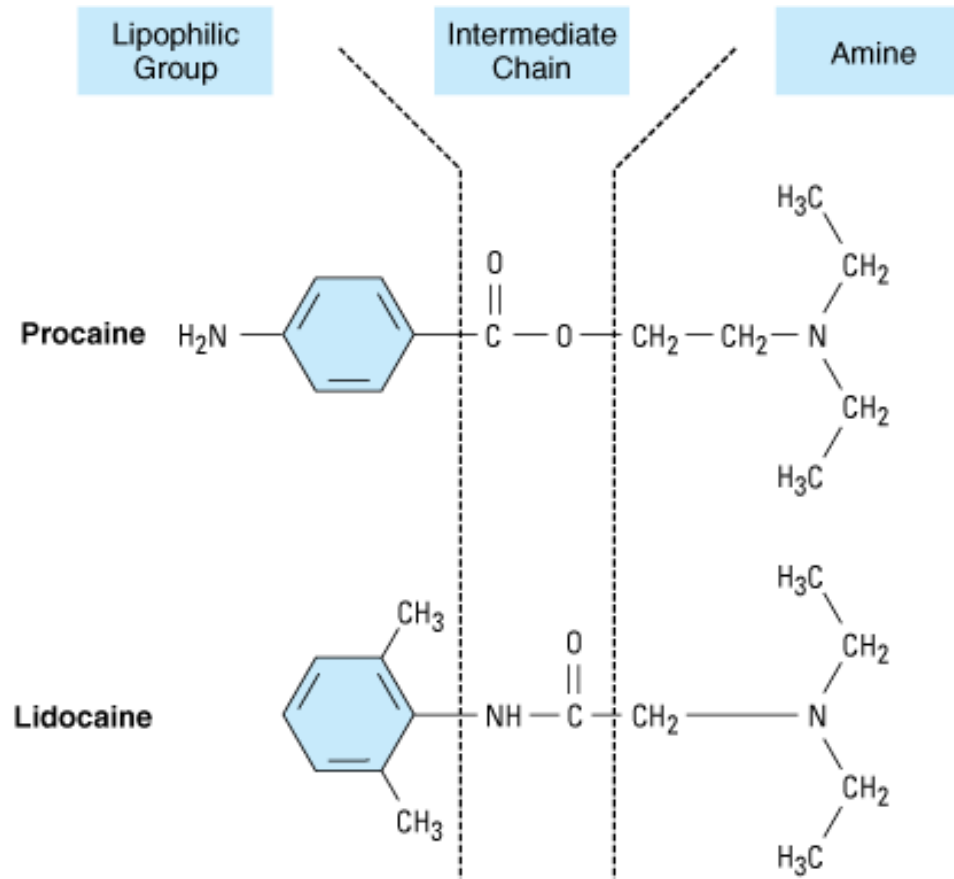


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# LA – routes of administration



- **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>

# 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 patients treated with betalytics,  $\text{Ca}^{2+}$  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

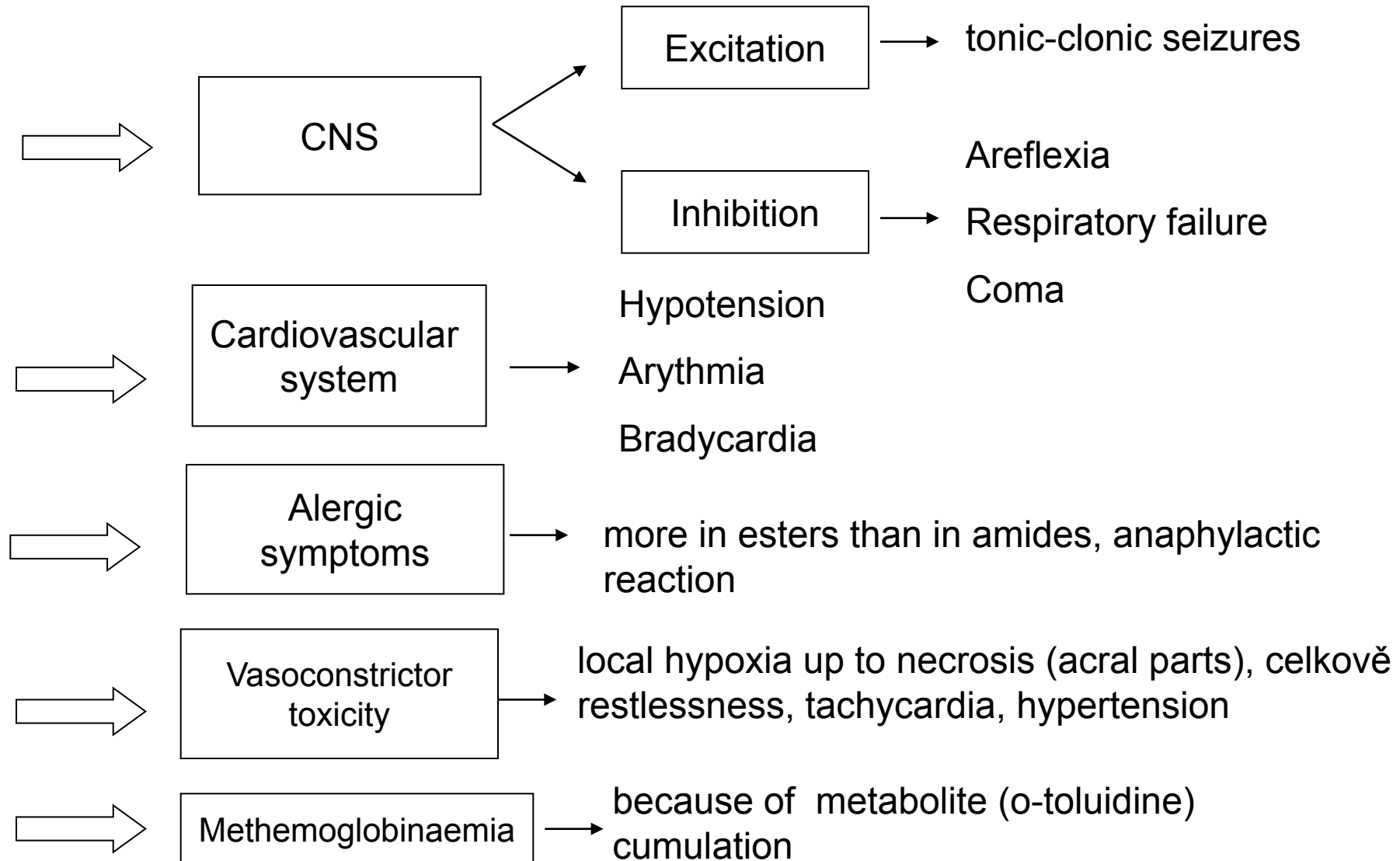
- intermediate

  - 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



# Allergic 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% substitutive 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 cardiovascular 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**