Local Anesthetics

Ideal mixtures

**JRC mixture**:

lidocaine 1% - 10-20 mL

bupivacaine 0.25% - 10 mL

bicarbonate 8.4% (1 mEq/ml) - 4 mL

chemistry

lipophilic group-intermediate chain-ionizable group

 ↑ ↑

frequently aromatic ring usually tertiary amine

Classes

Two classes of local anesthetics (according to intermediate chain):

1. **Aminoesters** (s. “esters”) – hydrolyzed by ***plasma*** pseudocholinesterase – shorter duration of action.
2. **cocaine** – first agent (isolated in 1860 by Niemann); used *only topically* on mucous membranes; blocks uptake of catecholamines at adrenergic synapses → hypertension; produces euphoria / dysphoria (abuse potential).
3. **procaine** (synthesized in 1905 by Einhorn)
4. **tetracaine**
5. **benzocaine** - used *only topically*.
6. **Aminoamides** (s. “amides”) – hydrolyzed in ***liver*** (contraindicated in liver dysfunction; use procaine!)
7. **lidocaine** – most popular prototype drug (synthesized in 1943 by Löfgren); also may be used as antiarrhythmic agent i/v.
8. **prilocaine** – may produce MetHb.
9. **etidocaine**
10. **mepivacaine**
11. **bupivacaine** – may produce cardiac arrest!
12. **dibucaine** – potent long-acting, with systemic toxicity (used only topically).

Properties

**pKa** - pH at which 50% drug exists in basic uncharged form and 50% in cationic form.

* lower pKa - faster onset (some agents, such as chloroprocaine, can be given at much higher concentrations, thereby offsetting effects of high pKa).

**Hydrophobicity** - associated with *greater potency* (smaller & more lipophilic molecule – greater potency).

**Protein binding** - correlates with *longer duration of action*.

| **Drug** | **Relative Conduction-Blocking Potency** | **Physiochemical Properties** |
| --- | --- | --- |
| ***pK*a**  | ***Hydrophobicity*** |
| **Low potency, short acting** |
|   Procaine | 1 | 8.9 | 100 |
| **Intermediate potency** |
|   Mepivacaine | 1.5-2 | 7.7 | 130 |
|   Prilocaine | 1.8-3 | 8.0 | 129 |
|  Cocaine | 2 |  |  |
|   Lidocaine | 2-4 | 7.8 | 366 |
|   Chloroprocaine | 3 | 9.1 | 810 |
| **High potency, long acting** |
|   Tetracaine | 8-16 | 8.4 | 5,822 |
|   Bupivacaine | 8-16 | 8.1 | 3,420 |
|   Etidocaine | 8-16 | 7.9 | 7,320 |
|  Ropivacaine |  |  |  |

Mechanism of Action

- reversible **blockade of voltage-dependent Na+ channels** in nerve fibers → nebevyksta neuronų depoliarizacija → nebeplinta impulsas išilgai aksono.

1. ***specific receptor theory*** – drug displaces Ca2+ from site near Na+ channel and then blocks Na+ channel.
2. ***membrane expansion theory*** – drug (being lipophilic) incorporates into membrane, preventing opening of pores.
* *small unmyelinated fibers* (pain, temperature, autonomic activity) are most sensitive:
1. complete analgesia for surgical procedures

N.B. pain is first sensation to disappear!

1. sympathetic vasoconstriction↓↓↓ (e.g. permanent catheters to treat ischemic limbs; but systemic hypotension in “high spinal block”)
* *thick, heavy myelinated* (type Aα) *motor fibers* are least sensitive, but at higher concentrations, motor activity is also paralyzed (e.g. respiratory paralysis in “high spinal block”).

N.B. in *large nerve trunks*, ***motor fibers*** are usually located circumferentially – exposed to anesthetic first (motor block before sensory block)!

N.B. in *extremities*, ***proximal sensory fibers*** are located in mantle of nerve trunk and are blocked before ***distal sensory fibers*** (located in core of nerve trunk) – anesthesia first develops proximally and spreads distally.

* normally **do not cause CNS depression**.
* drug molecule first must penetrate membrane (function of lipophilic portion); in acidic environment (e.g. inflamed tissues) almost all drug molecules are ionized (retard drug membrane penetration);
* drug solutions are made acidic (hydrochloride salts pH 4-6) – salts are buffered in tissue to physiologic pH – more uncharged drug molecules (only **uncharged drug molecules can penetrate membranes**); repeated injections → local tissue buffers depletion → tachyphylaxis.
* inside cell drug must be ionized - only **charged (cationic) drug form is active**!
* mixing solutions with *sodium bicarbonate\** (to raise pH) is associated with ***less burning*** on infiltration and ***more rapid onset of action*** (CO2 diffuses into cells and lowers intracellular pH – retards charged [cationic] drug molecules inside cells).

\*1 ml per 10 ml lidocaine, 0.1 ml per 10 ml bupivacaine

Applications & Doses

| **Medication** | **Applications** | **Nerve Block** | **Duration (min)** | **Onset (min)** | **Maximal Dose (mg)** |
| --- | --- | --- | --- | --- | --- |
| ***Infiltration*** | ***Spinal*** | ***Epidural*** | ***Without Epinephrine*** | ***With Epinephrine*** |
| Chloroprocaine | -- | -- | + | + | 20-45 |   5-15 | 800 | 1000 |
| Lidocaine | + | + | + | + | 45-75 |   5-15 | 300(4.5 mg/kg q 90 mins) |   500(7 mg/kg q 90 mins) |
| Mepivacaine | + | -- | + | + | 45-75 |   5-15 | 400 |   550 |
| Bupivacaine | + | + | + | + | 90-180 | 15-30 | 175 q 3 hrs |   225 3 hrs |

1% lidocaine has 10 mg/mL;

**30 ml of 1% lidocaine may be used safely in average adult**;

if more volume is required - use 0.5% lidocaine (up to 60 ml).



**TAC mixture** (tetracaine, adrenaline, cocaine) – for *topical* application.

* effectiveness is visible by appearance of skin blanching.
* in experiments, using this mixture increased infection rates in contaminated wounds.

**EMLA (eutectic mixture of local anesthetics)** – lidocaine 2.5% + prilocaine 2.5%; applied *topically* 60-90 min before procedure; requires overlay of occlusive dressing; safety in open wounds not established.

Toxicity

Toxicity depends on systemic absorption:

1. **site of injection** (when used for regional anesthesia);
* *inadvertent intravascular injection* produces toxicity with much smaller doses.
* in spinal anesthesia drug may be combined with 10% dextrose (to increase specific gravity – solution becomes heavier than CSF).
1. **speed of absorption**.
2. toxicity correlates to **drug potency**.
3. **CNS** (earliest signs of overdose or inadvertent intravascular injection): numbness / tingling of tongue / lips, metallic taste, light-headedness, tinnitus, visual disturbances → slurred speech, disorientation, convulsions, respiratory depression → death.
	* lidocaine and cocaine can produce changes in mood and behavior.
4. **Cardiovascular system** (at higher doses - anestetikai užblokuoja miocitų Na+-channels) - cardiovascular collapse (myocardial depression & vasodilation).
	* + except cocaine – causes vasoconstriction and hypertension; vasoconstriction is useful to decrease bleeding from mucosa in topical application;
		+ most cardiotoxic is bupivacaine.
5. **Allergic reaction** (rare) – ***only for “esters”*** (metabolized to p-aminobenzoic acid - may cause allergic reactions).

Some (e.g. topical benzocaine) may cause methemoglobinemia!

Toxicity Prevention

To prevent local anesthetic toxicity is clinical priority!

1. knowledge of **maximal safe dose**.
2. premedication with diazepam (0.1-0.2 mg/kg) may prevent seizures.
3. **aspiration** to detect unplanned vascular entry.
4. ***epinephrine*** - slows absorption:
	* decreased toxic response secondary to rapid absorption;
	* prolonged duration of action (≈ doubled).

treatment of toxicity

1. **Oxygen & airway support** (hyperventilation is useful!).
2. **Benzodiazepine** (e.g. midazolam) or **thiopental** - if seizure does not terminate spontaneously.
3. **Cardiovascular support**.

N.B. cardiovascular toxicity from bupivacaine is particularly difficult to treat.

* bupivacaine is racemic mixture of *levo*- and *dextro*-isomers; levobupivacaine (only *levo*-isomer) is less cardiotoxic.

*Panaudota literatūra*:

Sabiston Textbook of Surgery 2001

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B.G.Katzung “Basic and Clinical Pharmacology” 1987