Local anesthetics agents

Done by:
Asal Alsayyed
Yara saleh
Areej Alhadidi
Lecture Objectives:

1. Definition
2. Classification of Local Anaesthetic Agents
   2.1. Comparison between the two Classes.
3. Mode of action
4. Preparation of Local Anaesthetic Agents
5. Addition of Vasoconstrictors
   5.1. Indications and Contraindications and Dosage.
   5.2. How can I prepare Adrenaline 1:200000?
6. Clinical uses of local anesthetic agents
7. Lidocaine
8. Toxicity (Causes, Prevention and Treatment)
   8.1. Systemic Toxicity
Definition:

✓ Local anaesthetic agents: can be defined as drugs which are used clinically to produce reversible loss of sensation and in a circumscribed area of the body.

✓ LA block generation, propagation, and oscillations of electrical impulses in electrically excitable tissue.

✓ Clinically used local anesthetics consist of:

  lipid soluble, substituted benzene ring, linked to amine group via alkyl chain containing an amide or linkage.
Classification of LA agents:

There are 2 classes of local anaesthetic drugs defined by the nature of the intermediate chain.

I. The amide LA agents include:
- lidocaine
- Prilocaine
- ropivacaine
- etidocaine
- bupivacaine
- mepivacaine

II. The ester LA agents include:
- Cocaine
- Chloroprocaine
- Procaine
- Tetracaine
There are important practical differences between these 2 groups of LA agents

- Esters are relatively **unstable** in solution, Amides are relatively **stable** in solution
- Esters are rapidly hydrolysed in the body by plasma cholinesterase (and other esterases)
- Amides are slowly metabolised by hepatic amidases
- Esters: One of the main breakdown products is para-amino benzoate (PABA) which is associated with allergic phenomena and hypersensitivity reactions
- Amides: hypersensitivity reactions to amide local anaesthetics are extremely rare
- In current clinical practice esters have largely been superseded by the amides.
- Esters: Short duration of action and less intense analgesia, while amides are longer duration of action and more intense analgesia.
Mode of action:

- After injection, the tertiary amine base is liberated by the relatively alkaline pH of tissue fluids:
- These effects are due to blockade of sodium channels, thereby impairing sodium ion flux, across the membrane
- It limits influx of sodium, thereby limit propagation of action potential
- In clinical practice, local anaesthesia may be influenced by the local availability of free base, as only the unionised portion can diffuse through the neuronal membrane. Thus, local anaesthetics are relatively inactive when injected into tissues with an acid pH (e.g. pyogenic abscess), which is presumably due to reduced release of free base.
- Na+ ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to Na+ that is required for an action potential
- When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain
- Delivery techniques include topical administration, infiltration, peripheral nerve blocks, and neuraxial (spinal, epidural, or caudal) blocks
Pharmacodynamics

- Sodium channel blocker
- Only non-ionized (free base) form can penetrate neuron membrane
- Critical length
Pharmacokinetics

- ↑ blood flow
- ↑ lipid solubility/hydrophobicity
- ↑ protein binding
- ↓ pKa
  - Mepivacaine: 7.6
  - Lidocaine, prilocaine, articaine: 7.8
  - Bupivicaine: 8.1

shorter duration of action
more potent
longer duration of action
longer duration of action
faster onset of action
**Sensory and Motor fibers are sensitive - depends on fiber size, type, and myelination;:

- Smaller fibers are more sensitive than larger ones.
- Myelinated nerves are blocked earlier than non-myelinated ones.
- Autonomic fibers are more susceptible than somatic ones.
- *Order of blockade in general is : Pain - temperature - touch - deep pressure.*
Composition:

- Local anesthetic agent: lidocaine HCl 2%
- Vasoconstrictor: adrenaline 1:80000
- Reducing agent: sodium metabisulphite 0.5 mg. This act as a preservative for the vasoconstrictor
- Preservative: methylparaben 0.1%
- Isotonic solution: sodium chloride 6mg
- Fungacide: thymol
- Vehicle: ringer's solution - minimize discomfort during injection
- Diluting agent: distilled water
- To adjust pH: sodium hydroxide
- Nitrogen bubble: 1-2mm in diameter and is present to prevent O2 from being trapped cartridge and potentially destroying the vasopressor or vasoconstrictor
What does 1% Lidocaine mean?

The dilute preparations are presented as percentage (%) solutions of LA.

-A solution expressed as 1% contains 1g substance in each 100ml.

1 g in 100 ml = 1000mg in 100 ml = 10 mg in 1 ml

-The number of mg/ml can easily be calculated by multiplying the percentage strength by 10. Therefore a 0.25% solution of lidocaine contains 2.5mg/ml of solution (10 * 0.25=2.5 mg /ml)

As an example: 2% lidocaine?

2%=2 gram/100ml = 2000mg/100ml=20mg/1ml

So 2% solution has 20mg/ml
Another way to look at it

• Take the % of solution and put a (zero) behind it
• 2% concentration=20mg/ml
• 3%concentration=30mg/ml
• 4%concentration=40mg/ml
Vasoconstrictors:

*Vasoconstrictors are the chemical agents added to local anesthetic solutions to oppose vasodilatation caused by these agents and to achieve hemostasis.

*Adrenaline is the most commonly used vasoconstrictor in concentrations ranging from 1 in 80,000 to 1 in 300,000
Actions:

- The addition of a vasoconstrictor to a local anesthetic agent causes constriction of blood vessels and thereby controls tissue perfusion.

- The net effects caused by addition of vasoconstrictors to anesthetic agents are:
1. It decreases the blood flow to the site of injection, because of vasoconstriction.

2. It decreases the rate of absorption of local anesthetic agent into cardiovascular system.

3. It lowers the plasma level of local anesthetic agent thereby, decreasing the risk of systemic toxicity of local anesthetic agent.

4. Higher volumes of local anesthetic agent remain in and around the nerve for longer periods, thereby increasing the duration of action of most local anesthetic agents

5. It decreases bleeding at the site of injection because of decreased perfusion. This is useful when increased bleeding is expected during a surgical procedure
CONTRAINDICATIONS OF LOCAL ANESTHETICS WITH VASOCONSTRICTOR:

1) Hypertension (>200/110)
2) Ischemic heart disease.
* Acute myocardial infarction in the last 6 months
* Anginal episodes at rest
3) Arrhythmias.
* Cardiac dysrhythmias that are refractory to drug treatment
4) Uncontrolled DM and thyrotoxicosis.
* In DM, microcirculatory changes will result in impaired blood flow to the tissues. The inclusion of a vasoconstrictor in local anesthetic solution may further compromise the inadequate blood supply, and result in local ischemia and tissue sloughing
5) Already using MOA (monoamine-oxidase inhibitors), tricyclic antidepressants (TCAs).
6) Should not be used in proximity to end arteries: (fingers, toes, penis, nose tip, ear lobules)

*End artery (or terminal artery) is an artery that is the only supply of oxygenated blood to a portion of tissue.

7) Epinephrine should not be used during GA when a patient is receiving an inhalational halogenated anesthetic agents such as halothane, methoxyflurane, and ethrane. These vasoconstrictors cause cardiac dysrhythmias.

8) It is not indicated in pregnant patients because of its potential oxytocic actions.
Clinical Uses of Local Anaesthetics:

1- surface anesthesia
2- infiltration anesthesia
3- spinal anesthesia
4- epidural anesthesia
5- nerve block
6- Field block
7- regional anesthesia
1-topical application:
*to skin for analgesia or mucous membranes
*most useful and effective: Lidocaine and prilocaine

2-infiltration:
dilute solution of local anesthetic is administered under the skin, this blocks the sensory nerve endings (no action on the motor function), usually used for minor procedures like incision, hydrocele, and herniorrhaphy.

*Most useful and effective: Lidocaine, prilocaine, mepivacaine, and Bupivacaine
3-Spinal Anesthesia:
* Injection directly into the subarachnoid space (CSF btw L2-L3 or L3-L4)
* The primary site of action is the nerve roots in cauda equina and due to this injection the lower limb and pelvis get paralyzed and anesthetized
* This technique is usually used for operation on lower limb, pelvis and abdomen
* Most useful and effective: hyperbaric Bupivacaine 0.5% or lidocaine

4-Epidural anesthesia:
* The local anesthetic is injected into epidural space (between dura mater and the lig flavum) which usually acts on nerve roots and produces multiple paravertebral blocks
* Most useful and effective: isobaric Bupivacaine 0.5% or lidocaine (2.0%)
Lidocaine

*amide-type local anesthetics and it is the most common local anesthetics that uses nowadays
*Lipo-philic, widely distributed into the body
*it has rapid onset of action (in IV injection ...within 3-5 min )
*The half-life of lidocaine is 90 min to 120 min in most patients.
(This may be prolonged in patients with hepatic impairment because It metabolizes in the liver (p450 system))
*Protein binding 60-80%
*It is completely eliminated by the kidney after about 9 hr
Duration of action:

- Spinal: 1-1.5 without Epi
- Epidural: 2hr without Epi / 3hr with Epi
- IV injection: 15-30 min
- IV regional anesthesia: tourniquet time
- Peripheral nerve block: 1hr without Epi / 3hr with Epi
*Lidocaine mixed with a small amount of epinephrine is available to allow larger doses for numbing, and to make the numbing effect last longer

*pH of plain solution-6.5 while pH of vasoconstrictor containing solution-5.0-5.5
Mechanism of action:

Lidocaine use in anesthesia can be explained by the fact that it alters depolarization in neurons, by blocking the fast voltage gated sodium (Na+) channels in the cell membrane. With sufficient blockade, the membrane of the presynaptic neuron will not depolarize and so fail to transmit an action potential, leading to its anesthetic effects. Careful titration allows for a high degree of selectivity in the blockage of sensory neurons, whereas higher concentrations will also affect other modalities of neuron signalling.
Action:

**ON CNS:**

*Blocks conduction around a nerve*
- Initially causes drowsiness & lethargy
- Higher doses cause excitation followed by depression

**On CVS:**

Blood vessels: vasodilation in the injected area
Medical uses:

1. local anesthesia:
   *Spinal & epidural anesthesia
   Longer-acting substances such as bupivacaine are sometimes given preference for them; lidocaine, though, has the advantage of a rapid onset of action

   Epidural: ideal for obstetric anesthesia

   *preinduction:
   - Blunt the stress response to intubation
   - 1.5 g/kg given 3-5 min prior to laryngoscopy

   *to blunt the pain of propofol
   - 2 ml of 1% lidocaine in 18 ml of propofol

   *in dental procedures & minor surgery
**Lidocaine is used *topically* to relieve itching, burning and pain from skin inflammations.

2. *antiarrythmic drug:*
   
it is used *intravenously* for the treatment of *ventricular arrhythmias* if amiodarone is not available or contraindicated.

*Lidocaine should be given for this indication after defibrillation, CPR, and vasopressors have been initiated.*
Routes of administration:

**Intravenous injection**
(sometimes combined with epinephrine)

**Dermal patch**
(sometimes combined with prilocaine)

**Nasal instillation/spray**
(combined with phenylephrine)

**Topical gel**
Adverse effects:

**Adverse drug reactions are rare when lidocaine is used as a local anesthetic and is administered correctly.**

**Most ADRs associated with lidocaine for anesthesia related to administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia, and allergic reactions only rarely occur.**
- **CNS excitation**: nervousness, agitation, anxiety, tingling around the mouth (*circumoral paraesthesia*), headache, hyperesthesia, tremor, dizziness, pupillary changes, hallucinations, and seizures

- **CNS depression with increasingly heavier exposure**: drowsiness, slurred speech, hypoesthesia, confusion, loss of consciousness, respiratory depression.

- **Cardiovascular**: hypotension, bradycardia, arrhythmias, and/or cardiac arrest.[1]

- **Respiratory**: bronchospasm, dyspnea, respiratory depression or arrest

- **Gastrointestinal**: metallic taste, nausea, vomiting

- **Ears**: tinnitus

- **Eyes**: local burning, visual changes

- **Skin**: itching, depigmentation, rash, edema, bruising, inflammation of the vein at the injection site, irritation of the skin when applied topically

- **Allergy**
Contraindications:

- Heart block, second or third degree (without pacemaker)
- Serious adverse drug reaction to lidocaine or amide local anesthetics
- Concurrent treatment with quinidine, flecainide, disopyramide, procainamide (class I antiarrhythmic agents)

*they inhibit of the cytochrome P450 enzyme and can lead to increased blood levels of lidocaine
Toxicity from local anesthetic drugs

Causes:
1. Accidental rapid intravenous injection.

2. Rapid absorption, such as from a very vascular site e.g. mucous membranes. Intercostal nerve blocks will give a higher blood level than subcutaneous infiltration, whereas plexus blocks are associated with the slowest rates of absorption and therefore give the lowest blood levels.

3. Absolute overdose if the dose used is excessive.

**Note:**
It involves the CNS and CVS. In general (CNS) is more sensitive to LA than the CVS. Therefore CNS manifestations tend to occur earlier. Brain excitatory effects occur before the depressant effects.
CNS signs & symptoms:

**Early or mild toxicity:** lightheadedness, dizziness, tinnitus, circumoral numbness, confusion and drowsiness.

( Patients often will not volunteer information about these symptoms unless asked)

**Severe toxicity:** tonic-clonic convulsion leading to progressive loss of consciousness, coma, respiratory depression, and respiratory arrest.
CVS signs & symptoms:

**Early or mild toxicity:**
- if LA with Adrenaline ... tachycardia with Hypertension
- If no Adrenaline ... bradycardia with hypotension

**Severe toxicity:**
- Collapse due to the depressant effect of the LA acting directly on the myocardium (e.g. Bupivacaine)
- Severe and intractable arrhythmias can occur with accidental IV injection.
Prevention:

- Monitor ECG, O2 saturation

- Always have adequate resuscitation equipment and drugs available before starting to inject
Treatment:

✓ stop the injection and assess the patient.
✓ Call for help while treating the patient
✓ Treatment is based on the ABCDE of Basic Life Support
  * Ensure an adequate airway, give O2 in over facemask.
  * Ventilate the patient if there is inadequate spontaneous respiration
  * Intubation: if the patient is unconscious and unable to maintain an airway.
✓ Administering a 20% lipid emulsion infusion (lipid rescue therapy) is a valuable asset.
Tx of circulatory failure:

- with I.V fluids and vasopressors:
  - **Ephedrin**
  - **Adrenaline** If ephedrin is not available or not effective in correcting the hypotension

- Treat arrhythmias & **Start CPR** if cardiac arrest occurs.
- Treat Convulsions with **anticonvulsant** drugs
Thank you