Local anaesthetic agents
Lecture Objectives:

1. Definition

2. Classification of Local Anaesthetic Agents
   2.1. Comparison between the two Classes.

3. Mode of action

4. Composition of Local Anaesthetic Agents
Lecture Objectives

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

Ehab Kharabsheh

7. Lidocaine

8. Toxicity (Causes, Prevention and Treatment)
   8.1. Systemic Toxicity
The Pharmacology of Local Anaesthetic Agents (LA) Awn Khawaldeh

A substances which reversibly inhibits nerve conduction when applied directly to tissues, thereby producing temporary loss of sensation in a limited area.

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

Classification:
The molecule of the clinically useful LA agents consists of
1. A tertiary amine (hydrophilic group) attached to an
2. Aromatic ring (lipophilic group) by an

Figure 13.13
Representative structures of ester and amide anesthetics.
There are important practical differences between these 2 groups of LA agents

<table>
<thead>
<tr>
<th>Ester</th>
<th>Amide</th>
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<tbody>
<tr>
<td>• Short duration of action</td>
<td>• longer lasting analgesia.</td>
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<tr>
<td>• Less intense analgesia</td>
<td>• Produce more intense analgesia.</td>
</tr>
<tr>
<td>• Higher risk of hypersensitivity because the metabolism of most</td>
<td>• Rarely cause hypersensitivity reactions</td>
</tr>
<tr>
<td>ester produce PABA (a known allergen)</td>
<td>• Not hydrolyzed by Plasma Cholinesterase, more slowly metabolized</td>
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<tr>
<td>• metabolized by Plasma pseudocholinesterase in blood.</td>
<td>by liver microsomal P 450 enzymes.</td>
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<tr>
<td>• Rarely used for Infiltration anesthesia</td>
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<tr>
<td>• But useful for topical anesthesia on mucous membranes.</td>
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</table>

For there reasons amides are more commonly used
Classification of LA Agents

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

<table>
<thead>
<tr>
<th>Ester</th>
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<tr>
<td>Cocaine</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Procaine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Chlorprocaine</td>
<td>Mepivacaine</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Prilocaine</td>
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<tr>
<td></td>
<td>Ropivacaine</td>
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All LA cross BBB and placenta
Common Uses Of Local Anaesthetics:

- Dentistry
- Dermatology
- Excision
- Spinal Anaesthesia
Mode of action - Membrane structure

1. Resting Potential
   - $\text{Na}^+/\text{K}^+$ pump

2. Depolarisation
   - Voltage-gated $\text{Na}^+$ channel

3. Repolarisation
   - Voltage-gated $\text{K}^+$ channel

4. Resting Potential
   - $\text{Na}^+/\text{K}^+$ pump

Graph:
- Membrane potential (mV) vs. Time (msec)
- Key points:
  - 1. Resting Potential
  - 2. Depolarisation
  - 3. Repolarisation
  - 4. Resting Potential
  - Threshold at -55 mV
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.

✓ **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.
ACTIONS OF LA - LOCAL

• All LAs have effects on nerves acting via Na+ channel - sensory endings, nerve trunks, NM junctions, ganglion and receptors.
• 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.*
IMPORTANT CLINICAL PROPERTIES OF LOCAL ANESTHETICS

1. pKa = ONSET
pKa = pH at which 50% of drug is ionized
Only the nonionized form crosses into the nerve cell (inside the axon will become ionized so block Na channel)

2. pH influence
- Decrease in pH (solution more acidic) shifts equilibrium toward the ionized form, delaying the onset action.
- Presence of Pus and inflammation will retard the action of LA.

3. LIPID SOLUBILITY = Potency
Higher solubility => can use a lower concentration and reduce potential for toxicity [LA], because 90% of the nerve cell membrane is composed of lipid.

4. PROTEIN BINDING = Duration
- Bupivacaine 95%
- Lidocaine 65%
Composition of LA Solution

- Lignocaine Hcl (Anesthetic)
- Adrenaline (Vasoconstrictor) *(don’t explain Lama will do)*
- Sodium metabisulphite (Reducing Agent)
- *methyl parahydroxybenzoate* (Preservative)
- Thymol (Fungicide) *(in the past some solution tend to become cloudy duo to the proliferation of minute fungi)*
- Salts (NaCl) (Isotonicity) *(minimize discomfort during injection)*
- Distilled Water (Vehicle)
- OR Ringer’s Lactate

- reducing agent *(e.g. sodium metabisulphite)* to enhance the stability of added vasoconstrictors *(unstable on solution)*
- Preservative for stability of anesthetic
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 100mls.

Lidocaine 1% means a 1:100 dilution.
That is 1 g : 100ml;
That is 1000 mg : 100ml
That means 10 mg : 1ml.

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)
• 2 ml of Lidocaine 1% with 1:100,000 epinephrine has how many mg of lidocaine and how many mg of epinephrine?

1- 2ml of the solution will contain 2* (10mg) = 20 mg of lidocaine
2- Epinephrine 1:100,000 means
   1g : 100,000 ml
   1000mg : 100,000 ml, or
   1mg : 100ml
   0.01mg : 1ml, or
   2ml of the solution will contain 2* (0.01mg) = 0.02mg of epinephrine

2ml of lidocaine 1% and Epinephrine 1:100,000 has 20mg of lidocaine and 0.02mg of epinephrine
Most LA produce some degree of vasodilation, and they may be rapidly absorbed after local injection.
Why we add vasoconstrictors

Addition of a vasoconstrictor to a local anesthetic may have several beneficial effects:

1) a decrease in the peak plasma concentration of the local anesthetic agent, so decrease the systemic toxicity and increase the safety margin of local anaesthetics by reducing their rate of absorption

2) increase in the duration and the quality of anesthesia

3) reduction of the minimum concentration of anesthetic needed for nerve block

4) decrease of blood loss during surgical procedure

Adrenaline is the most commonly used vasoconstrictor in concentrations ranging from $1 \text{ in 80,000}$ to $1 \text{ in 300,000}$.
How can I prepare Adrenaline 1:200000?

>>> Adrenaline dilution 1:200000 means
1 g in 200000 ml = 1000 mg in 200000 ml
1 mg in 200 ml = 0.1 mg in 20 ml

>>> How can I prepare Adrenaline 1:80000 ..............

= 0.1 mg in 8 ml
contraindication for Adrenaline containing local anaesthetic agents:

• Absolute contraindication (should never be used) for:

  1. infiltration around end-arteries

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

i.e. ring block of fingers, penis or other areas with a terminal vascular supply as the intense vasoconstriction may lead to severe ischaemia and necrosis
2. Intravenous regional anaesthesia (IVRA) is an anesthetic technique on the body's extremities where a local anesthetic is injected intravenously and isolated from circulation in a target area.

A tourniquet is applied to a limb proximal to the planned surgical site, and a local anesthetic is injected intravenously distal to the tourniquet.

Relative contraindication:

1. Patient with severe hypertension
   - Tourniquet use is associated with an increase in systolic blood pressure over time; this increase may be excessive, particularly in hypertensive patients.

2. General anaesthesia with halothane

Reduce bp dec pulse rate >ischemia
Clinical Uses of Local Anaesthetics

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<td>1.</td>
<td>Topical Anaesthesia</td>
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<td>2.</td>
<td>Infiltration Anaesthesia</td>
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<td>3.</td>
<td>Peripheral Nerve Blockade</td>
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<td>4.</td>
<td>Intravenous regional anaesthesia (IVRA)</td>
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<tr>
<td>5.</td>
<td>Spinal Anaesthesia</td>
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<tr>
<td>6.</td>
<td>Extradural Anaesthesia</td>
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</table>
• **1: Topical Anaesthesia**

LA may be applied to the skin, the eye, the ear, the nose and the mouth as well as other mucous membranes. Most useful and effective: Lidocaine (i.e. gel 2%) and prilocaine (i.e. EMLA)

**2: Infiltration Anaesthesia**

Provide anaesthesia for minor surgical procedures. Commonly used Amide LA are (Lidocaine, prilocaine, mepivacaine and Bupivacaine). The site of action is at unmyelinated nerve endings and onset is almost immediate.
3: Intravenous regional anaesthesia (IVRA)

IVRA (BIER s Block) analgesia for minor surgical procedures. The local anaesthetic agent is injected into a vein of a limb that has been previously exsanguinated and occluded by a tourniquet.

The site of action is probably the unmyelinated nerve fibres, Prilocaine and Ldocaine are commonly used.

⚠️ Bupivacaine and etidocaine should never be used for IVRA!

They are significantly protein bound and once the tourniquet is released there is a risk of cardiotoxicity. Several deaths have been reported during IVRA with bupivacaine.
Lidocaine

• Lidocaine, the first amino amide-type local anesthetic, was developed first by Löfgren and Lundqvist in 1943 and first marketed in 1948.

• Lidocaine Solutions 0.5, 1, 1.5 and 2% contain lidocaine hydrochloride 5, 10, 15 and 20 mg/mL, respectively. Solutions with epinephrine contain (1:100,000) or 0 (1:200,000) epinephrine.
Pharmacology

- Half life: (~90 min)
- Distribution: Lipo-philic, widely distributed into body
- pH of plain solution-6.5
- pH of vasoconstrictor containing solution-5.0-5.5
- Onset of action –rapid
- Pregnancy classification-B
- Effective dental concentration-2%
- Protein binding: 60-80 %
Lidocaine

• 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.
ACTIONS

• ON CNS
  • (i) Blocks conduction around a nerve

Anaesthesia
  • (ii) Initially causes drowsiness & lethargy
  • (iii) Higher doses cause excitation
  • followed by depression
ON CVS

Heart

Blood vessels

Abbreviates
Effective
Refractory
Period

Vasodilatation in the injected area
ROUTES OF ADMINISTRATION

- Intravenous injection
- (sometimes combined with epinephrine)
- Dermal patch (sometimes combined with prilocaine)
- Nasal instillation/spray (combined with phenylephrine)
- Topical gel
Lidocaine

• Lidocaine is a local anesthetic and antiarrhythmic drug.
• Lidocaine is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic, and in minor surgery.
ADVERSE EFFECTS

- Drowsiness
- Blurred vision
- Confusion
- Altered taste
- Tremors
- Tinnitus
CONTRAINDICATIONS

- Heart block
- Hypotension
- Bradycardia
- Lidocaine
- Quinidine
- Flecainide
- Disopyramide
- Procainamide
Toxicity from Local Anaesthetic Drugs

when excessive blood levels occur. usually due to:

1. Accidental rapid intravenous injection.

2. Rapid absorption, such as from a very vascular site ie 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.
Signs and Symptoms of LA Toxicity

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: light-headedness, 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:** Usually about 4 - 7 times the convulsant dose needs to be injected before CV collapse occurs. Collapse is 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.
Essential Prevention

- Monitor ECG, O2SAT
- Secure intravenous access before injection of any dose.
- 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 A B C D 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.
Treatment of circulatory failure

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

• Treat arrhythmias. Start chest compressions if cardiac arrest occurs.

• Treat Convulsions with *anticonvulsant* drugs (*Diazepam* 0.2-0.4mg/kg , *Thiopentone* 1-4 mg/kg)