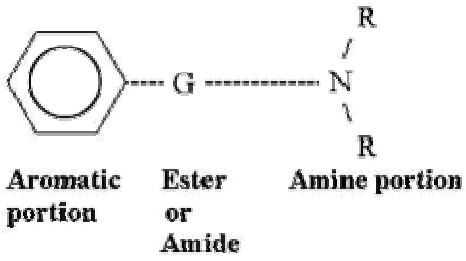
3.2 Local Anaesthetic Techniques

Local anaesthetic pharmacology and toxicity

LA Structure

- Most are weak bases - esters or amides - of the form:



  Long G groups have increased toxicity, shorter ones have less potency (as a rule).

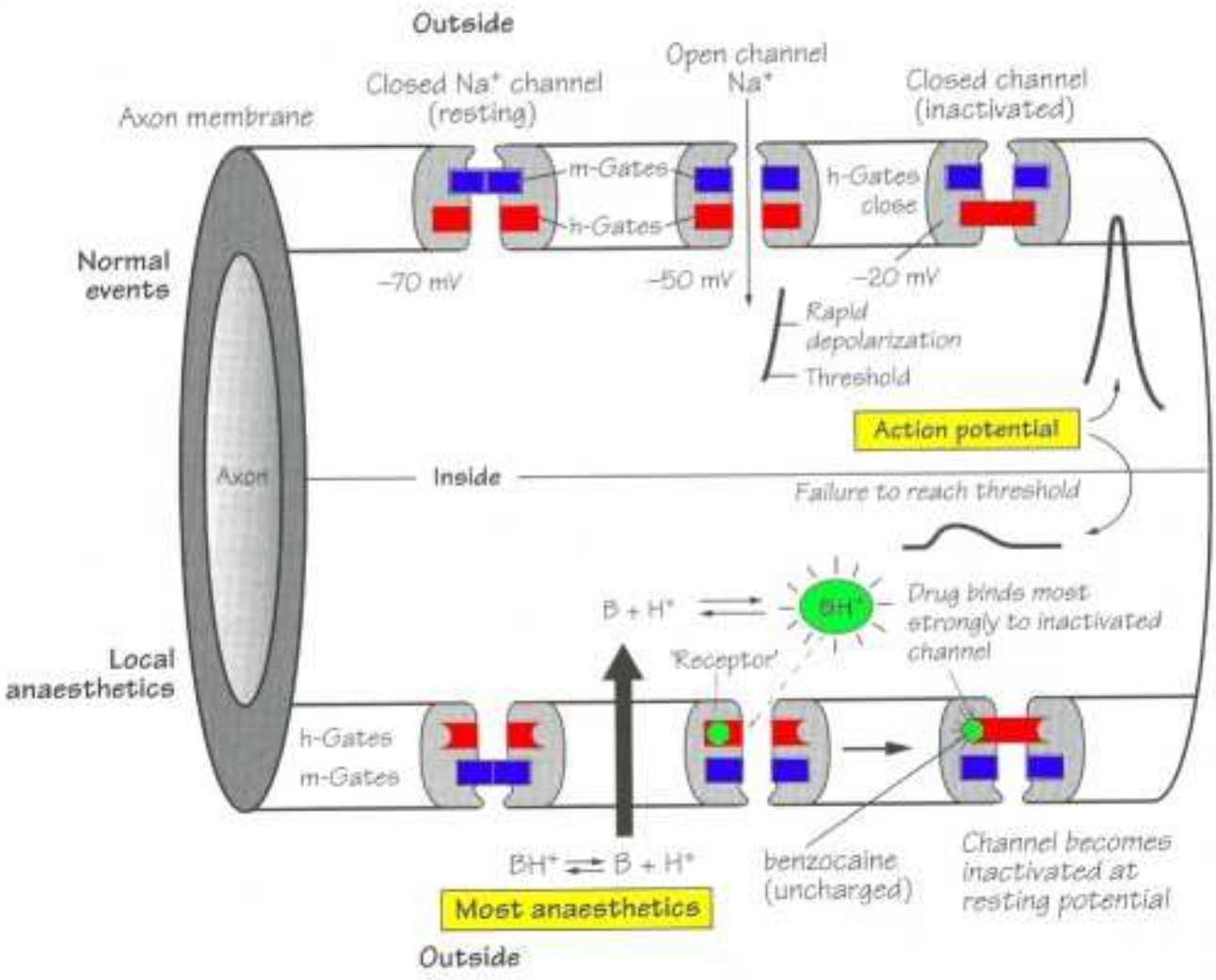
- Esters:
  - Cocaine – first extracted from Erythroxylon coca leaves (1860)
  - Procaine (1898)
  - Amethocaine
  - Chloroprocaine
- Amides:
  - Lignocaine - synthesised in 1943 (WWII)
  - Prilocaine
  - Bupivacaine
  - Mepivacaine
  - Ropivacaine

LA Uses

- Conduction Anaesthesia
  - Cutaneous nerve block - topical (EMLA, ALA), or infiltration
  - Minor nerve blockade (e.g. ulnar, radial or intercostal)
  - Major blockade with wide dermatomal distribution (e.g. brachial plexus blockade).
  - Amide LA have rapid onset for minor nerve blockade and more variable onset for major nerve blockade
  - Duration of anaesthesia determined by the total dose of the drug
- Epidural Anaesthesia
  - LA is deposited in epidural space between dura mater and periosteum lining the vertebral canal

    - This space contains adipose tissue, lymphatics and blood vessels
    - The injected LA produces blocks intradural spinal nerve roots
    - Quality and extent of the blockade determined by the volume and total dose of the drug.
    - Bupivacaine (0.5%) is commonly used for epidural anaesthesia
- Spinal Anaesthesia
    - LA is introduced directly into CSF
    - Faster onset of action and a smaller dose (about a tenth) than that needed for epidural anaesthesia.
    - Solutions of lignocaine (5%), prilocaine (5%) bupivacaine (0.5%) and mepivacaine (4%) are used to produce spinal anaesthesia.
- Intravenous regional anaesthesia e.g. Bier's block
- Other non-anaesthetic uses:
    - Lignocaine used in ventricular tachycardia
    - Increases the threshold for ventricular fibrillation

Mode of Action



In resting neurones a selectively permeable cell membrane and non-diffusible cellular anions leads to a negative membrane potential maintained by the Na+/K+ ATP pump. Transmembrane voltage-gated Na+ channels are closed.

Nerve stimulation starts depolarizing the membrane. If threshold is reached, Na+ channels become activated, and rapid Na+ influx & depolarisation ensues..

The increased membrane potential deactivates the Na+ channels which close as the conductance of K+ out of the cell increases and the membrane repolarises. This action potential is unidirectional as recently open Na+ channels are briefly inactivated (refractory).

LAs are weak bases (pKa ~ 8-9) and the ionised (BH+) and non-ionised (B) forms present in ECF in relative proportions given by the Henderson-Hasselbach Equation:

$$pH = pKa + \log([B]/[BH+]$$

At physiological pH, the ratio is 10-100:1 in favour of BH+ and as the pH lowers this ratio and the [BH+] increases.

However it is only the non-ionised form (B) that can diffuse through the lipophilic cell membrane & enter the nerve, but it needs to be ionised again before blocking (stereoscopically or via a receptor) the Na+ channels (preferentially those in an inactivated state) from the inside.

Pharmacodynamics

- Differential block: Smaller diameter fibres are generally affected first (e.g. C and A-delta pain fibres) before larger (e.g. motor) nerves (except where the motor fibres may surround sensory fibres in large nerve bundles).
- If equal size then myelinated fibres more sensitive than unmyelinated
- Potency and duration proportional to lipophilicity
- At low pH (such as inflamed tissue) less LA penetrates the nerve as most is in the charged form and LAs are less effective.
- Action potential conduction brings more sodium channels into the inactivated state and thus increases the rate of the block (use dependency).

Pharmacokinetics

- Absorption: Depends on site, vascularity, vasoconstrictor use, pH & degree of tissue-binding.
- Distribution: Amides – initially in highly perfused organs then redistributed to fat; Esters – not studied as metabolised too quickly
- Metabolism: Esters hydrolysed rapidly by pseudocholinesterase (except cocaine) & liver esterases; Amides by liver microsomal dealkylation - variable first pass metabolism.

- Excretion: Renal - acidification of the urine promotes excretion (by ion trapping). Protein-binding is proportional to duration of action.

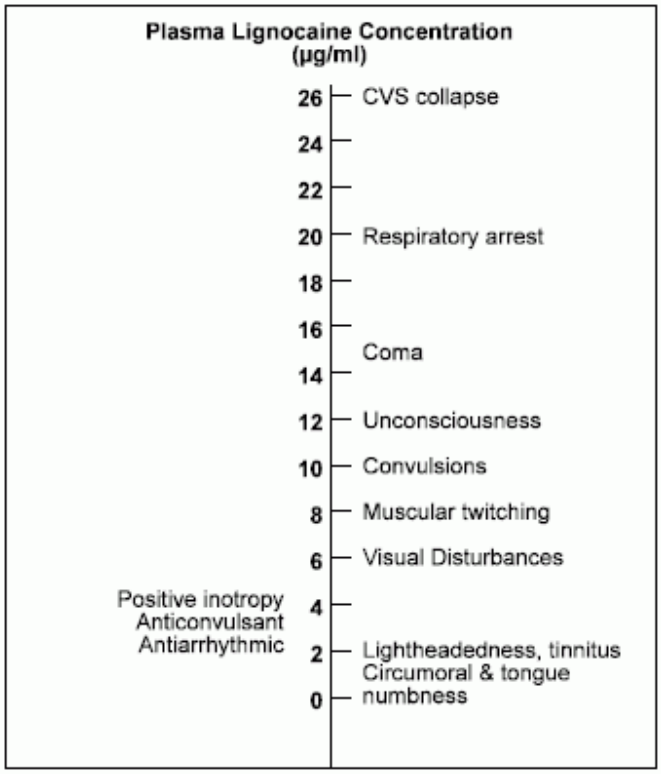
Use With Adrenaline

- Adrenaline is a local vasoconstrictor
- Reduced blood supply has three advantages:
    - Less bleeding at the site [local infiltration]
    - Less systemic absorption, and consequently lower toxicity and opportunity of giving a higher dose
    - Prolonged duration of action
- More useful with short acting agents such as lignocaine
- In the past it was always advised that adrenaline should never be used for infiltration around end-arteries i.e. penis, ring block of fingers due to potential risk of severe ischaemia and necrosis. Reviews of the literature have debunked this myth and support the safe use of 1:100,000 or more dilute formulations in these areas if there is no pre-existing circulation impairment and good technique is followed. Caution is still advised if full ring blocks are to be performed.
- Also contraindicated in thyrotoxicosis, arrhythmias, CCF, IHD.
- NB. Cocaine is a LA with vasoconstrictor properties

Topical Use

- Eyes - Amethocaine drops
- Skin (for venepuncture, cannulation, LP, etc.)
    - EMLA: Eutetic mixture[1] of local anaesthetics (lignocaine & prilocaine)+emulsifiers
        - Available as 5% cream or 1g patch. Generally restrict to 1-2 patches per child < 1yr
        - Need to wait 45mins - 1 hr under occlusive dressing.
        - Not sterile thus shouldn't be used on open wounds
        - Can make veins less visible
        - Increased risk of methaemoglobinaemia with age<6 months
    - Amethocaine gel (AnGel)
        - Available as 4% preparation
        - Need to wait 30-45mins, remove after maximum of 1 hr
        - Can cause a dermatitis (metabolises to PABA)
        - Not sterile thus shouldn't be used on open wounds
    - ALA or LET: Adrenaline, lignocaine & amethocaine (tetracaine)
        - Can be used on open wounds
    - TAC:Tetracaine (amethocaine), adrenaline & cocaine
        - Not used much now due to cocaine

Adverse Effects & Toxicity



- Local pain on injection – warm and buffer with 8.4% bicarbonate in 1:10 ratio & inject slowly with smallest needle.
- Systemic effects can occur with intravascular injection or tissue absorption of an excessive dose. The effects are related to site of injection, LA used, abs blood level, rate of change of blood level & pre-existing disease.
- Allergic reaction/Dermatitis - Notably with esters as they metabolise to PABA
- Neurological
    - Initially: circumoral/tongue paraesthesiae or numbness, tinnitus, nystagmus & dizziness
    - Then CNS excitation: restlessness, tremor, fits
    - Finally CNS depression: confusion, coma
- Cardiovascular - occur usually after CNS signs:
    - Excitation (HR, BP & CO)
    - Arrhythmias
    - Depression (decreased myocardial excitability, profound hypotension)
    - Regarding bupivacaine: less 'safety margin between first CNS and CVS effects, VF is a major risk, also CVS collapse may be particularly refractory.
- Respiratory depression
- Methaemoglobinaemia with prilocaine (esp. foetus/young infants)

Contraindications

- Known allergy - can use diphenhydramine (antihistamine with LA properties) instead if infiltration required.
- Amide LAs should be avoided in severe liver disease or if patient has inhibition of liver cytochrome P450 3A4 enzyme or is on drugs that compete for this enzyme: e.g. Chloramphenicol, Erythromycin, Fluconazole, Cimetidine, Midazolam. Note that beta blockers can reduce liver blood flow and so slow metabolism

Summary of doses:

Drug	Plain dose	Dose with adrenaline
Lignocaine	3-5mg/kg	7mg/kg
Bupivacaine	2mg/kg	3mg/kg
Prilocaine	6mg/kg	8mg/kg
Ropivacaine	2.5mg/kg	4mg/kg

References:

1. Dunn R. The Emergency Medicine Manual 3rd Ed.
2. Katung B. Basic & Clinical Pharmacology 8th Ed.
3. Cameron P. et al. Textbook of Adult Emergency Medicine 2nd Ed.
4. Mahadevan S. & Garmel G. An Introduction to Clinical Emergency Medicine
5. Neal M. Medical Pharmacology at a Glance 3rd Ed.

Footnote:

1. Eutetic Mixture = A mixture whose constituents are in such proportions that it melts and solidifies at a single temperature that is lower than the melting point of the constituents or any other mixture of them.