Pharmacology of Local Anaesthetic drugs

Local Anaesthetics

- Lidocaine hydrochloride (*Xylocaine*)
  - Lidocaine hydrochloride + 1:200,000 adrenaline
- Bupivacaine hydrochloride (*Marcain*)
  - Bupivacaine hydrochloride + 1:200,000 adrenaline
- Mepivacaine (*Scandonest*)
- Prilocaine (*Citanest*)
- Levo-Bupivacaine (*Chirocaine*)
- Ropivacaine (*Naropin*)

LAs prevent generation of nerve impulses (action potentials) in pain fibres

- Injected LA diffuses into nerve fibre
  - LA molecule blocks Na^+channels in nerve fibre membrane
  - Nerve impulse cannot be generated
- LA gradually diffuses out of the nerve fibre
- Nerve function returns to normal
  - Impulse can be generated and propagated
- LA taken up from site of injection into general circulation
- LA metabolised in liver and excreted via kidney

How Local Anaesthetics Work: 1

- **Normal (non-anaesthetised) state:**
  - Stimulus to the nerve (fibre OR ending) $\rightarrow$ Na^+ channels open in nerve membrane
  - Na^+diffuses down a concentration gradient from interstitial fluid, into nerve
  - **Unstable membrane**
    - *nerve impulse generated at periphery*
    - *pain perceived centrally*

How Local Anaesthetics Work: 2

- **LA drug administered**
  - LA molecules diffuse through nerve membrane
  - LA molecules combine with protein in nerve membrane forming the Na^+ channels $\rightarrow$ blockage of channel
- **Stable nerve membrane**
  - *No nerve impulse / action potential generated locally*
  - *No pain perceived centrally*
  - *Vasodilatation*
  - *Eventual loss of voluntary muscle contraction*

Characteristics of excitable cells
e.g.: Nerve tissue

- **Potential difference (~70 mvolts) across cell membrane**
  - **Concentration of Na^+ is**
    - **high outside the cell (i.e.: in tissue fluid)**
    - **low inside the cell (i.e.: in nerve cytoplasm)**
- **Membrane stimulus provokes a predictable and specific 'all or nothing' electrical reaction by the cell**
  - **Membrane pores open**
  - **Na^+ flows down concentration gradient into cell**
    - **Equalizes charge either side of membrane**
    - **Upsets resting state condition (less +ve outside cell)**
- **Upsets adjacent membrane areas**
  - **Wave-like membrane instability and movement of ions across membrane**
  - **Generation of nerve impulse / muscle contraction**

The Refractory Period

- **Influx of +ve ions across the cell membrane equalizes the charge on either side of the cell membrane**
  - The membrane in that area becomes temporarily stable, non-excitable and non-responsive to further stimulus
- **Cell membrane remains stable and non-reactive until the base-line ionic concentrations (inside and outside the excitable cell) have been restored**.
  - Na^+ are 'pumped' out of the cell back into the tissue fluid, across the membrane, against the ionic gradient
  - This is known as the **refractory period, and normally lasts only milliseconds**
- **Once the base line state has been restored** (i.e.: a high concentration of Na^+ in tissue fluid and a low concentration of Na^+ within the nerve cell) **that area of cell membrane can once again react to a stimulus.**
- **LA administration causes a prolonged refractory period in the nerve**

Onset of Action

- Lidocaine hydrochloride = 5 mins
- Bupivacaine hydrochloride = 20 mins
- Mepivacaine = 10 mins
- Prilocaine = 10 mins
- Levo-Bupivacaine = 20 mins
- Ropivacaine = 10-30 mins

Duration of Action

- Lidocaine = 1-2 hours
  - Lidocaine + 1:200,000 adrenaline = 2-4 hours
- Bupivacaine = 6-8 hours
  - Bupivacaine + 1:200,000 adrenaline = 12-16 hours
- Mepivacaine = 2-4 hours
- Prilocaine = 2-4 hours
- Levo-Bupivacaine = 5-15 hours
  - Up to 30 hours post-op analgesia
- Ropivacaine = 4-8 hours
  - Up to 24 hours post-op analgesia

Cautions

- Do not inject adrenalinised solutions into the distal foot
  - Causes ischaemia
  - ‘Chemical tourniquet’
  - Ischaemic effect persists for duration of anaesthesia
- Avoid adrenalinised solutions in patients taking
  - Beta-blockers
  - MAOIs
  - Tri-cyclic anti-depressants

Calculation (in mg) of total LA dose administered from drug labelled as % solution

- Percentage Mass
  - 1% solution = 10mg of drug in 1ml
  - 2% solution = 20 mg of drug in 1ml
  - 3% solution = 30mg of drug in 1ml
- THUS
  - 3.5ml of 1% soln delivers 35mg of drug
  - 8.3ml of 2% soln delivers 166mg of drug
  - 5.6ml of 3% soln delivers 168mg of drug

Maximum safe doses
70Kg or >70Kg person

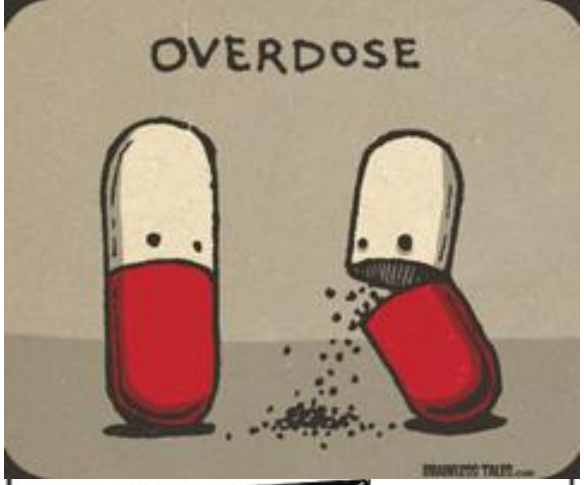
- Lidocaine
  - 200mg (3mg / Kg)
  - 20ml of 1% OR 10ml of 2% soln
- Bupivacaine / Levobupivacaine
  - 150mg (2mg / Kg)
  - 30ml of 0.5% OR 60ml of 0.25% soln
- Mepivacaine OR Prilocaine
  - 400mg (6mg /Kg)
  - 13ml of 3% soln
    - NB: ***MSD Mepivacaine for child = 3mg /Kg***
- Ropivacaine
  - ~250mg (4mg/Kg)
  - 50ml of 0.5% OR 33ml of 0.75% soln

Maximum Safe Dose for patient <70kg

- MSD of 1% Lidocaine for 68kg person?
  - MSD for 70kg = 200mg
  - MSD for 68kg in mg = 68/70*200 = 195mg
  - *MSD of 1% Lidocaine soln for 68kg, in ml = 195/10 = 19.5ml*
- MSD of 3% Mepivacaine for 61kg person?
  - MSD for 70kg = 400mg
  - MSD for 61kg in mg = 61/70*400 = 349mg
  - *MSD of 3% Mepivacaine soln for 61kg, in ml = 349/30 = 11.6ml*
- MSD of 0.5% Bupivacaine for 58kg person?
  - MSD for 70kg = 150mg
  - MSD for 58kg in mg = 58/70*150 = 120mg
  - *MSD of 0.5% Bupivacaine soln for 58kg, in ml = 120/5 = 24.25ml*

ADRs of LA

- Toxicity (Type A ADR)
  - High plasma concentration
    - Actual overdose
    - Relative overdose
- Faint
  - Vasovagal attack
    - Psychosomatic effect
- Hypersensitivity reactions
  - Rare with amide-type LAs



"We don't have to anesthetize patients anymore. I just walk in with this and they pass out in a second."

Toxic Effect of LAs

- CNS effects
  - Inebriation, Lightheaded-ness, Drowsiness
  - Numbness of tongue / peri-oral tissues, Paraestheiae
  - Restlessness, Nausea + vomiting, Blurred vision
  - Muscle twitching, Tremors, Convulsions
  - Respiratory failure, Coma
- Cardiovascular effects
  - Myocardial depression
  - Peripheral vasodilatation
  - Hypotension and Bradycardia
  - Arrhythmias and Cardiac arrest

Lidocaine (Lignocaine) plain MSD for a 56Kg child?

- MSD Lidocaine = 3mg drug per Kg body mass
  - MSD for this patient = 3x56 = 168mg in total
- 10mg in 1ml of 1% solution
  - MSD = 168/10 of 1% lidocaine = 16.8ml
- 20mg in 1 ml of 2% solution
  - MSD = 168/20 of 2% lidocaine = 8.4ml

Mepivacaine (Scandanest) plain MSD for a 78Kg adult?

- MSD Mepivacaine = ~ 6mg drug / Kg body mass
  - MSD for this patient = 6x78 = **400mg in total**
- 10mg in 1ml of 1% solution
  - MSD = 400/10 of 1% mepivacaine = 40ml
- 20mg in 1 ml of 2% solution
  - MSD = 400/20 of 2% mepivacaine = 20ml
- 30mg in 1 ml of 3% solution
  - **MSD = 400/30 of 3% mepivacaine = 13ml**

Bupivacaine plain
MSD for a 65Kg adult?

- MSD Bupivacaine = 2mg drug per Kg body mass
  - MSD for this patient = 2x65 = 130mg in total
- 10mg in 1ml of 1% solution
  - MSD = 130/10 of 1% bupivacaine = 13ml
- 5mg in 1 ml of 0.5% solution
  - MSD = 130/5 of 0.5% bupivacaine = 26ml
- 2.5mg in 1 ml of 0.25% solution
  - MSD = 130/2.5 of 0.25% bupivacaine = 52ml

Prilocaine (Citanest) plain MSD for a 62Kg adult?

- MSD Prilocaine = ~ 6mg drug / Kg body mass
  - MSD for this patient = 6x62 = 372mg
- 10mg in 1ml of 1% solution
  - MSD = 372/10 of 1% prilocaine = 37ml
- 20mg in 1 ml of 2% solution
  - MSD = 372/20 of 2% prilocaine = 18ml
- 40mg in 1 ml of 4% solution
  - **MSD = 372/40 of 4% prilocaine = 9ml**

Be cautious in using LAs on these patients

- Children, elderly or debilitated patients
- Impaired cardiac conduction
- Cardiovascular disease
- Hypovolaemia
- Shock
- Impaired respiratory function
- Epilepsy
- Myaesthenia gravis

Contra-Indications to LA

- Inflamed / infected tissues
  - Reduced anaesthetic effect
  - Increased rate of absorption predisposes to toxicity
- Patients with heart block

- Adrenalinised LA solutions
  - Never into a digit
    - Risk of ischaemic necrosis
  - Not with severe hypotension
  - Not with unstable cardiac rhythm (e.g.: uncontrolled AF)
  - Not with MAOIs and tricyclic antidepressants

Drug Interactions and Local Anaesthetics

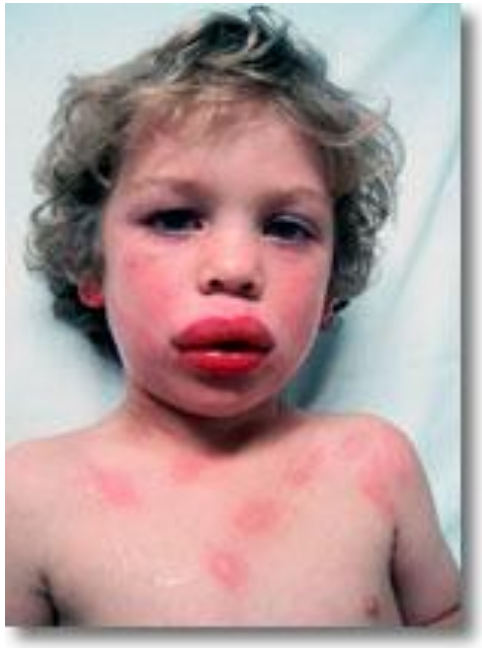
- Lidocaine + Cimetidine
  - Lidocaine metabolism reduced / plasma concentration increased
- Lidocaine / Bupivacaine / Levo-bupivacaine / Prilocaine / Ropivacaine + Propanolol / Amiodarone
  - Increased myocardial depression
- Lidocaine + antivirals
  - Increased plasma concentration of lidocaine
- Lidocaine + Loop and Thiazide Diuretics
  - Lidocaine effectiveness reduced
- Mepivacaine + opioid sedatives
  - Increased risk of LA toxicity

Drug Interactions and Local Anaesthetics, Contd

- Lidocaine + bupivacaine
  - Increased risk of LA toxicity
  - Total dose should not exceed combined MSDs
- Prilocaine + dapsone
  - Methaemoglobinaemia
- Ropivacaine + Fluvoxamine (Anti-depressant)
  - Ropivaciane metabolism inhibited
- Levo-bupivacaine + TCAs or MAOIs
  - Increased risk of LA toxicity

Anaphylaxis (Type B ADR)

- Drugs: Antibiotics (LAs = rare)
  - Immunologically mediated response
  - Tends to increase with repeat exposure
- Angio-oedema
  - Breathing difficulties (stridor)
  - Hives
  - D+V; abdominal cramps
- Severe hypotension
  - Loss of consciousness
  - Death
- Management
  - Administer adrenaline
    - **0.5ml (0.5mg) 1:1000 adrenaline,**
    - **Repeated after 5 mins as necessary**
    - **999**



Adrenaline

Epinephrine (Adrenaline)

- Hormone secreted by the adrenal medulla
  - Catecholamine
- Sympathetic neurotransmitter
  - Nonselective agonist of all (α1, α2, β1, β2, and β3) adrenergic receptors
- Participates in the fight or flight response
  - Increases blood glucose levels
    - α-adrenergic receptors: inhibits pancreatic insulin secretion, stimulates pancreatic gluconeogenisis, and skeletal glcyolyisis
    - β-adrenergic receptors: triggers pancreatic glucagon secretion. increases pituitary ACTH secretion, and increases adipose lypolysis
  - Increases heart rate
  - Constricts blood vessels and increases blood pressure
  - Dilates bronchi and bronchioles
  - Increases skeletal muscle contraction

Epinephrine (Adrenaline) Contd.

- Adverse reactions to adrenaline include
  - Palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, hypertension and acute pulmonary oedema
  - Contraindicated in people on non-selective beta-blockers
- Drug of choice for treatment of anaphylaxis
  - Administered as 1:1000 dilution
  - 0.5mg / ml IM, repeated if necessary 5mins later
- Vasoconstrictor action in LA
  - Pre-mix 1:200,000 dilution
  - Reduced dose / prolonged action
  - CI for LA is distal part of the foot
  - CI for patients on MAOIs