

### Q3 Outline the factors which affect the onset, duration of action and toxicity of local anaesthetic agents.

Local anaesthetics – agents used to inhibit transmission of painful afferent signals to the cortex. Act by entering the cell in the unionized form, converting to the ionized form and then blocking the Na channel from the inside. May also diffuse into the cell membrane and swell, pushing the channel shut.

#### FACTORS AFFECTING ONSET OF ACTION

- Onset of action will depend on Fick's law of diffusion  $J = \frac{-P \times SA \times \Delta C}{t}$   
Where P = permeability constant. Dependent on:
  1. Particle characteristics –
    - Lipophilicity (more lipid soluble drugs will diffuse faster)
    - Particle size (smaller particles diffuse more quickly – relevant for topical LAs)
    - pKa (degree of ionization will affect diffusion as only unionized particles can cross cell membrane – as LA's are weak bases with pKa generally greater than 7.4, they are mostly ionized at pH 7.4)
  2. Membrane characteristics
    - Presence of transporters will increase onset speed
    - Lipid nature of membrane
    - pH of surrounding tissue – infected tissue is generally more acidic and will reduce the fraction of unionized drug even further

SA = surface area of membrane over which drug is diffusing (larger surface area = more rapid onset)

T = thickness of membrane (thicker membrane = slower onset)

$\Delta C$  = the greater the concentration gradient, the faster the onset

#### FACTORS AFFECTING DURATION OF ACTION

- Protein binding → LA's with limited protein binding have a shorter duration of action
- Vasoconstrictors → duration of action of an LA is proportional to the amount of time it spends at the nerve axon
- Regional blood flow → an increase in flow will remove drug from the effect site more quickly
- Metabolism → ester LA's (procaine, amethocaine) are metabolised via plasma esterases to inactive compounds and generally have a shorter half life than the amides, which are metabolized in the liver. Liver dysfunction or reduced hepatic blood flow will reduce the metabolism of these agents and thus prolong the duration of action.

#### TOXICITY

- Signs of toxicity may be seen at plasma lignocaine concentrations of 2mcg/ml (tinnitus, circumoral numbness), progressing to convulsions at 10mcg/ml, respiratory arrest at 20mcg/ml and CVS collapse at 26mcg/ml.
- May be systemic (CNS and CVS), local tissue toxicity, allergic reactions or other effects
- Contributing factors include:
  - **Drug factors** – CNS: CVS ratio (dose ratio of CNS symptom onset (reversible) to CVS symptom onset (life threatening, refractory) is a measure of safety. Lignocaine 7, ropivacaine 4, bupivacaine 3), isomerism, lipophilicity, protein binding, pKa, coadministration with a vasoconstrictor, the dose administered and concentration, relative potency, and mechanism of action (all act via binding to and inactivating sodium channels, however bupivacaine is ten times slower at dissociating from the channel than lignocaine is)
  - **Patient factors** – cardiac output and regional blood flow, hepatic or renal dysfunction, blood pH and PaCO<sub>2</sub>
  - **Other factors** – site of injection, inadvertent IV injection, drug interactions