Pharm-06A5/Pharm-03B7/Pharm-00B13: Write short notes on factors affecting the speed of onset and duration of effect of local anaesthetics when used to produce peripheral nerve block. 89%/46%/54%

Peripheral nerve block and Local anaesthetics:

- Local anaesthetics (LA) produce transient and reversible conduction blockade along central and peripheral nerve pathways when applied in close proximity to them
- LAs are commonly used in peripheral nerve blocks → They are injected into tissue surrounding peripheral nerve/nerve plexuses → Achieve sensory and motor conduction blockade to facilitate surgery

Mechanism of LAs: *Antagonism of VG-Na^+ channels in excitable tissues*

- Unionised LA diffuses across the phospholipid membrane into the more acidic axoplasm and then becomes ionized → Ionised LA binds to the inner portion of the channel (H- or internal-gate of α-subunit) from within the cell
- Channel access and binding are dependent on its conformational state:
    - (i) LA gains access to its binding site within the channel ONLY when it is in its activated open state during an AP
    - (ii) LA then preferentially binds the channel during in its inactivated-closed state and maintains it in this state → Prevents reversion back to rested-closed state and activated-open state
- Antagonism of VG-Na^+ channels results in ↓ Na^+ permeability across the membrane → Slows the rate of rise in membrane depolarisation, and lowers the magnitude of membrane depolarisation → If $V_{THRESHOLD}$ is not met, then AP is not generated and impulse propagation is prevented ("conduction blockade")
- "Frequency-dependent blockade" → Nerve repeatedly stimulated is MORE sensitive to LA-induced conduction blockade than a nerve at rest → Because LA can only gain access to its binding site within VG-Na^+ channel to exert its effect when it is in an activated-open state during an AP

Factors that affect the speed of onset and duration of effect:

LA used in a peripheral nerve block obeys "Fick's Law of Diffusion":

- LA diffuses from injection site into the nerve fibres → then diffuses through nerve membrane to antagonise VG Na^+ channel
- Thus, speed of onset and duration of effect are governed by this law

$$J = \frac{A \times Sol. \times [\ ]_{GRADIENT}}{T \times \sqrt{Mwt}}$$

(1) Area (A) and Concentration gradient ($[\ ]_{GRADIENT}$):

- (i) ↑ LA dose (volume) → ↑ $[LA]_{GRADIENT}$ and ↑ area of nerve exposure to LA → Faster onset and ↑ duration of action
- (ii) ↑ potent LA (Ie. bupivacaine) → Lower volumes injected → Slower onset BUT ↑ duration of action
- (iii) Use of liposomal delivery systems or LMWT dextrans → Sustained LA release → Maintains $[LA]_{GRADIENT}$ and nerve area exposure to LA → ↑ duration of action
- (iv) Use of vasoconstrictor (Eg. Adrenaline) → ↓ regional blood flow 2° to vasoconstriction leads to ↓ systemic absorption → ↑ $[LA]_{GRADIENT}$ and ↑ area of nerve exposure to LA → ↑ duration of action
- (v) Intrinsic vasodilator activity of LA agent (prilocaine > lignocaine > bupivacaine > ropivacaine; cocaine causes vasoconstriction) – ↑ regional blood flow 2° to vasodilation leads to ↑ systemic absorption → ↓ $[LA]_{GRADIENT}$ and ↓ area of nerve exposure to LA → ↓ duration of action
- (vi) LA clearance

- Amide LA (and cocaine) are metabolised slowly in the liver → Accumulates in plasma → Attenuates absorption from injection site → ↑ $[LA]_{GRADIENT}$ and ↑ area of nerve exposure to LA → ↑ duration of action
- Ester LA are metabolised rapidly in plasma/liver by cholinesterases → Favours systemic absorption from injection site → ↓ $[LA]_{GRADIENT}$ and ↓ area of nerve exposure to LA → ↓ duration of action

> Note: A minimal length of myelinated fibre needs to be exposed to an adequate [LA] for conduction block to occur (at least 2-3 successive nodes of Ranvier or ~1 cm)

(2) Thickness (T) → Determined mainly by site of injection:
- Injection closer to nerve/nerve plexus → Faster onset of action
- Injection farther from nerve/nerve plexus (Ie. more soft tissue to penetrate) or topical application of LA → Slower onset of action

(3) Molecular weight of LA (Mwt) → Minimal effect as Mwt. are similar between LA agents

(4) Solubility (Sol.):
- (i) LA's lipid solubility → ↑ lipid soluble LAs will have:
  - ↑ absorption into injection site → Faster onset of action
  - ↑ potency → Less volume or [ ] given → Can slow onset of action (Bowman principle)
- (ii) LA's protein binding → ↑ lipid soluble LAs will have ↑ protein binding:
  - ↑ tissue protein binding → ↓ clearance from injection site by regional blood flow → ↑ duration of action
  - ↑ plasma protein binding → ↓ redistribution to other tissues, and ↓ clearance by metabolism and excretion → ↑ duration of action
- (iii) Ionisation state of LA
  - Determined mainly by (i) pKa of the LA and (ii) pH of the environment LA is in

$$pH = pKa + \log \frac{[B]}{[BH^+]}$$

  - LA are weak bases (pKa 7.6-8.9) that exists predominantly in its water-soluble ionised form at physiological pH
  - Fraction of unionised drug is ↑ with either a (i) low pKa LA (Eg. lignocaine) or (ii) high pH environment (Eg. alkalinisation with $NaHCO_3$) → Allows more LA to pass through excitable cell membrane → Faster onset of action LA
  - Fraction of unionised drug is ↓ with either a (i) high pKa LA or (ii) low pH environment (Eg. ischaemic/infected tissue, acidic adrenaline-containing solutions) → Less LA passes through cell membrane → Delayed onset of action

(5) Others factors:
- (i) Frequency-dependent blockade → Frequency nerve stimulation results in faster onset of block
- (ii) Impaired plasma cholinesterase activity (Eg. genetically-aberrant enzyme, drugs such as AChEi, SCh, Li, or disease such as CCF, liver disease, malnutrition, hypothermia, Etc.) → ↓ metabolism of ester LAs → ↑ duration of action
- (iii) Liver disease (Eg. cirrhosis) and/or ↓ HBF (Eg. GA, CCF, propanolol) → ↓ metabolism of amide LAs → ↑ duration of action
- (iv) Electrolyte imbalance (↓K^+ and ↓Ca^{2+}) → Antagonises conduction blockade → Faster onset and ↑ duration of action
- (v) Pattern of block (sensory, motor, autonomic) depends on:
  - Anatomical location of nerve fibre within mixed peripheral nerve (Ie. paralysis occurs early if motor nerve fibre is more peripheral than the sensory fibre)

    - Nerve sensitivity to LA (which is determined by nerve fibre size and myelination) → Small sensory (pain/temperature) and ANS fibres are blocked first then large proprioceptive and motor fibres
- (vi) Drug use – Opioids and steroids → Faster onset of action
- (vii) Pregnancy → Faster onset of action