

LOCAL ANAESTHETIC DRUGS

(a) *To describe the structure-activity relationships of local anaesthetic drugs.*

(c) *To describe the formulations of local anaesthetic drugs and their clinical importance.*

Introduction to Local Anaesthetic Drugs:

- Local anaesthetics (LA) are drugs that produce transient and reversible conduction blockade along central and peripheral nerve pathways when applied in close proximity to them
- There are two groups of LA drugs (classified according to their chemical structure):
 - o (1) Ester LA – Procaine, Chloroprocaine, Tetracaine (Amethocaine), Cocaine
 - o (2) Amide LA – Lignocaine, Etidocaine, Prilocaine, Dibucaine, Mepivacaine, Bupivacaine, Levobupivacaine, Ropivacaine

Preparations of Local Anaesthetic Drugs:

- LAs are weak bases (pKa 7.6-8.9) that are poorly soluble in water → Requires solubilisation in acidic environment as a HCl salt → ↑ % fraction of LA in its water-soluble ionised state
- Preparations of LA solutions are acidic with pH 3.9 to 6.5:
 - o HCl salt produces a pH ~ 6 – Acidic environment stabilises LA in solution as it promotes ↑ % fraction of LA in its water-soluble ionised state
 - o Sodium metabisulfite (preservative) can be added to adrenaline-containing LA solutions to produce a pH ~ 4 – This stabilises adrenaline by preventing its oxidative decomposition at more alkaline pH's

Note: LA solutions can be alkalinised with NaHCO₃ (to a final [] of 0.1M) to shorten onset (by 3-5 mins), and enhance depth and spread of nerve block:

- Since LAs are weak bases (pKa 7.6-8.9), the acidic solution minimises the fraction of LA in its unionised lipid-soluble form (3%) → Retards ability of LA to diffuse across lipid cell barriers to exert its effect
- Alkalinisation of LA solution thus increases the fraction of LA in its unionised lipid soluble form → Increases ability of LA to diffuse across cell membrane to cause effect

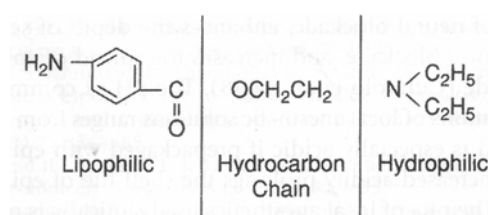
- Preservatives – Added as antimicrobial agents (methylparaben, fungicide) or to stabilise adrenaline-containing LA solutions (sodium metabisulfite)
- Vasoconstrictors (Adrenaline 1:200,000, phenylephrine, felypressin) – Can be added to attenuate absorption rate at injection site and prolong LA's duration of action
- Specific gravity of LA solution – Relevant for spinal anaesthesia as it determines spread of LA effect in subarachnoid space:
 - o Hyperbaric solution – Addition of glucose to LA solution → Increases its SG above CSF (SG 1.006-1.009) → LA will thus spread to more dependent areas
 - o Hypobaric solution – Addition of distilled H₂O to LA solution → Decreases its SG below CSF → LA will thus spread to less dependent areas
- Other additives:
 - o Liposomes – LAs can be incorporated into these to prolong their duration of action and decrease risk of systemic toxicity
 - o LMWT dextrans – Can be added to LA also decrease their systemic absorption and prolong their duration of action

Note: Ester LAs are comparatively unstable in solution cf. amide LAs (which can be stored for ~ 2 yrs)

Structure-Activity Relationships of Local Anaesthetic Drugs:

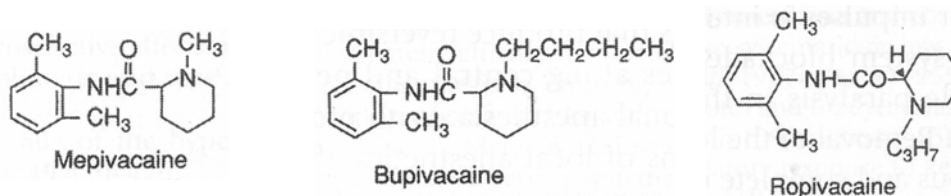
- LA drugs have a basic chemical structure consisting of:
 - o (1) Lipophilic group (usually a saturated aromatic ring; Eg. para-aminobenzoic acid) that confers LA activity
 - o (2) Hydrophilic group (usually a tertiary amine; Eg. diethyl amine)

- o (3) Hydrocarbon chain separating the lipophilic and hydrophilic groups
- o (4) Ester (-CO-) or amide (-NHC-) bond linking the hydrocarbon chain to the lipophilic group – Nb. This structure produces the two main groups of LA drugs



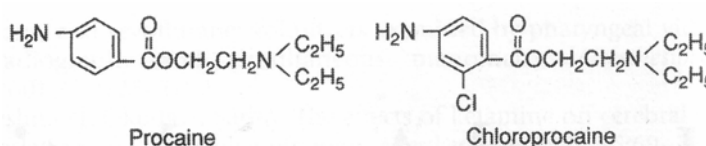
- Modification to this structure alters the pharmacology of the LA (Eg. lipid solubility, potency, duration of action, Etc.):
 - o (1) Total number of carbon atoms (length of hydrocarbon chain or alkyl group substitutions on aromatic ring or amine nitrogen) $\rightarrow$ $\uparrow$ C-atoms confers increased lipid solubility $\rightarrow$ $\uparrow$ potency, duration of action and onset of action

Eg. “Pipicoloxylidide” LAs are structurally identical with the exception of the alkyl group length on the piperidine N-group (amine) – (i) Mepivacaine has a methyl group (least lipid soluble/potent/toxic), (ii) Ropivacaine has a propyl group, and (iii) Bupivacaine has a butyl group (most lipid soluble/potent/toxic)



- o (2) Halogenation of aromatic ring $\rightarrow$ $\uparrow$ potency (due to $\uparrow$ lipid solubility) but $\downarrow$ duration of action (due to $\uparrow$ metabolism)

Eg. Chloroprocaine is procaine halogenated on the benzene ring



- o (3) Ester linkage $\rightarrow$ $\uparrow$ lipid solubility and potency (Eg. procaine vs procainamide)
- o (4) Ionisation state $\rightarrow$ $\uparrow$ fraction of unionised LA $\rightarrow$ faster onset of action

- The relative concentration of lipid-soluble unionised form (B) and water-soluble ionised form (BH^+) that exists at equilibrium is determined by (i) pK_a of the LA, and (ii) pH of the environment the LA is in

$$\text{pH} = \text{pK}_a + \log \frac{[\text{B}]}{[\text{BH}^+]}$$

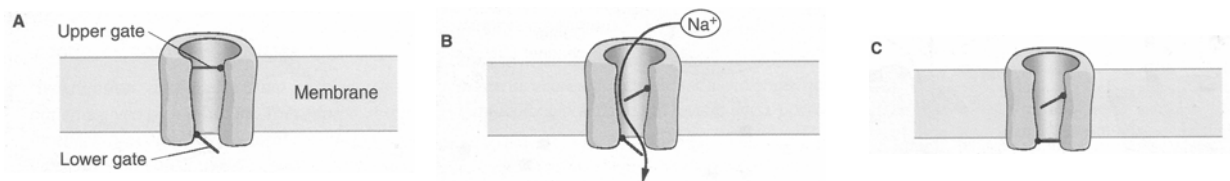
- LA are weak bases (pK_a 7.6-8.9) that exists predominantly in its water-soluble ionised form (I.e. $>50\%$ of LA carry +ve charge at tertiary amine group) at physiological pH
- Fraction of unionised drug is $\uparrow$ with either a (i) low pK_a LA (Eg. lignocaine) or (ii) high pH environment (Eg. alkalisation) $\rightarrow$ Allows more LA to pass through excitable cell membrane $\rightarrow$ Faster onset of action LA
- Conversely, fraction of unionised drug is $\downarrow$ with either a (i) high pK_a LA or (ii) low pH environment (Eg. ischaemic/infected tissue; acidic Adr-containing LA solutions) $\rightarrow$ Less LA passes through cell membrane $\rightarrow$ Delayed onset of action
- Within the axoplasm, the environment is acidic $\rightarrow$ Favours $\uparrow$ fraction of ionised drug which then binds avidly to the α -subunits of the VG Na^+ channel from inside the cell

- “Pipicoloxylidide LAs” (Eg. mepivacaine, bupivacaine, ropivacaine, levobupivacaine) are chiral drugs due to presence of asymmetric C-atom (Ie. exist as R- or S-isomers) – It is vital to note that isomers of these chiral drugs can vary in its pharmacology (esp toxicity):
 - Mepivacaine and Bupivacaine exist as racemic mixtures (50% S- and 50% R-isomers) → Associated with more CVS and CNS toxicity (due to presence of toxic R-isomers)
 - Ropivacaine and Levobupivacaine exist as pure S-isomers → Associated with less CVS and CNS toxicity than racemic mixtures (due to absence of toxic R-isomers)

(b) *To describe the mechanisms of action of local anaesthetic drugs.*

Voltage-Gated Na^+ Channel:

- An integral membrane protein consisting of:
 - o (i) A single α -subunit – Large polypeptide with 4 domains (D1 to D4) that forms a Na^+ -conducting pore, and a H-gate (“internal gate”) that modulates the flow of Na^+ across the pore and is the site of LA binding
 - o (ii) Varying numbers of adjacent smaller β -subunits – Modulate LA binding to the α -subunit
- Channel exists in three states
 - o (A) Rested-closed state (upper gate closed; lower gate opened)
 - o (B) Activated-open state (upper and lower gates opened)
 - o (C) Inactivated-closed state (upper gate opened; lower gate closed)



- Channel states during membrane depolarisation:
 - o At rest (I.e. nil membrane depolarisation) – Channels are distributed at equilibrium between inactivated-closed and rested-closed configurations → No Na^+ flux
 - o During AP (I.e. $V_{\text{THRESHOLD}}$ exceeded) – Conformational change and H-gate (upper gated) opened → Channel enters activated-open state briefly (0.7 msec only) and Na^+ influx occurs → Channel then quickly converts to inactivated-closed state and Na^+ flow ceases

Mechanism of Action of Local Anaesthetic Drugs:

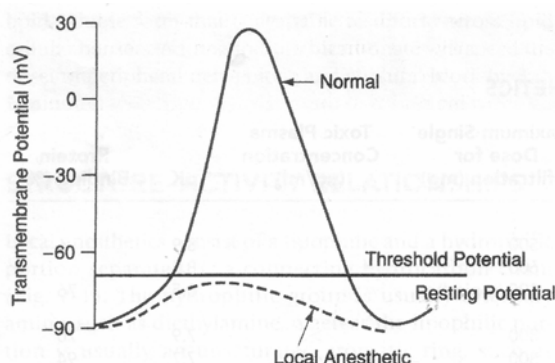
- (1) Main mechanism of action: Antagonism of VG- Na^+ channels in excitable tissues
 - o Unionised LA diffuses across the phospholipid membrane into the more acidic axoplasm and then becomes ionized → Ionised LA binds to the inner portion of the channel (H- or internal-gate of α -subunit) from within the cell (but can also obstruct the channel physically at its external opening)
 - o LA binding to the channel is dependent on its conformational state → LAs have a high affinity for binding to the channel in its activated-open and inactivated-closed states:
 - (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 inactivated-closed state and stabilises it in this conformation → Maintains channel in inactivated-closed state, and prevents reversion back to rested-closed state and activated-open state

Note: "Membrane expansion theory" is an alternate mechanism – Unionized lipid soluble LA dissolves into the phospholipid membrane and causes swelling of the lipoprotein matrix → Leads to disruption/inactivation of VG- Na^+ channel

- o Antagonism of VG- Na^+ channels results in ↓ Na^+ permeability and flow across the membrane → This (i) slows the rate of rise in membrane depolarisation, and (ii) lowers the magnitude of membrane depolarisation → Produces two effects:
 - $V_{\text{THRESHOLD}}$ is met (I.e. lower [LA]) – AP is still generated but will have a slower impulse conduction (I.e. decreased slope of phase 0 of AP)
 - $V_{\text{THRESHOLD}}$ is not met (I.e. sufficient [LA]) – AP is not generated and impulse propagation is prevented (“conduction blockade”)

Note: The RMP and Level of $V_{\text{THRESHOLD}}$ are NOT altered!

- LAs demonstrate “Frequency-dependent blockade”:
 - A nerve that is repeatedly stimulated (I.e. $\uparrow$ frequency AP generated) is MORE sensitive to LA-induced conduction blockade than a nerve at rest
 - This is because LA can only gain access to its binding site within the VG- Na^+ channel to exert its effect when the channel is in an activated-open state during an AP



- (2) Alternate mechanisms of action:
 - (a) Antagonise other VG channels (VG- K^+ channels and L-type Ca^{2+} channels), but with lower affinity than VG- Na^+ channels
 - (b) Also act on GPCRs

Local Anaesthetic Drugs: Differential Conduction Blockade

- Peripheral nerves consist of a mixture of ANS, sensory and motor nerve fibres:

Type	Size	Conduction velocity	Function
A α	Large (10-20 μm)	Fast (60-120 msec)	Motor
A β	Large (5-10 μm)	Fast (40-70 msec)	Sensory (touch, pressure)
A γ	Medium (3-6 μm)	Medium (15-30 msec)	Sensory (proprioception)
A δ	Medium (2-5 μm)	Medium (10-30 msec)	Sensory (pain, temperature)
B	Small (1-3 μm)	Slow (3-15 msec)	SNS preganglionic
C	Small (0.5-1 μm)	Slow (0.5-2 msec)	Sensory (pain, temperature)

- When LA is used during regional anaesthesia, the following general pattern of differential conduction blockade is observed as the [LA] used is increased. This pattern is observed due to the differences in sensitivities of different nerve fibre types within a peripheral nerve to the effects of LA:
 - (1) Autonomic impulses in SNS preganglionic nerve fibres are interrupted first (causing ANS blockade) as they are the most sensitive to LA
 - (2) Then somatic sensory impulses in sensory nerve fibres are interrupted (causing sensory anaesthesia) as they are moderately sensitive to LA
 - (3) Then somatic motor impulses in motor nerve fibres are interrupted last as they are the least sensitive to LA (causing skeletal muscle paralysis)
- Nerve sensitivity to LA is determined by:
 - (1) Axonal diameter (I.e. small fibres more sensitive to LA)
 - (2) Degree of myelination (I.e. unmyelinated fibres more sensitive to LA) – 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)

Note – More accurately the differential conduction blockade pattern is as follows:

- At low [LA] – Small diameter myelinated preganglionic SNS B-fibres are readily blocked $\rightarrow$ ANS blockade
- At higher [LA] – Small unmyelinated C-fibres and medium myelinated A δ fibres are blocked $\rightarrow$ Sensory blockade to pain and temperature only (Nb. Touch, pressure, proprioception and motor function retained!)
- At even higher [LA] – Large myelinated A γ , A β , and A α fibres blocked $\rightarrow$ Complete sensory and autonomic anaesthesia and skeletal muscle relaxation

Local Anaesthetic Drugs: Intrinsic Vasoactive Effect and Use of Vasoconstrictors

- LA drugs have intrinsic vasoactive activity:
 - At low concentrations, most LA drugs possess intrinsic vasodilator activity (prilocaine > lignocaine > bupivacaine > mepivacaine > ropivacaine)
 - At high doses, LA drugs tend to cause vasoconstriction (especially ropivacaine)

Cocaine is the ONLY LA drug that causes vasoconstriction at ALL concentrations!

- Effect of altered vasoactive activity on LA drugs:
 - Localised tissue vasoconstriction results in reduced systemic absorption of the LA drug → Maintains LA drug levels at injection site → Produces following effects:
 - (1) Increases the duration of LA activity at the injection site – Due to increased contact time of LA at injection site with nerve fibres
 - (2) Increases the potency of LA (Ie. effect of LA achieved at a lower dose) → Has a sparing effect on LA dose given
 - (3) Reduces risk of systemic LA toxicity – Reduces plasma [LA] 2° systemic absorption and lower dose needed to be delivered for effect
 - Localised tissue vasodilation results in the opposite effects (↑ systemic absorption → (i) Reduced duration of LA activity, (ii) Reduced LA potency, (iii) Increased risk of systemic LA toxicity)
- The aforementioned effects of localised tissue vasoconstriction can be achieved by adding a vasoconstrictor agent to the LA solution. Such agents include:
 - (1) Adrenaline (1:200,000 or 5 mcg/mL)
 - Vasoconstriction 2° to Adr is able to limit systemic absorption of LA drugs by ~ 33%. However, only select LA drugs (mainly lignocaine; but NOT bupivacaine, ropivacaine or levobupivacaine) have their effects prolonged by Adr – This is because more lipid soluble LAs are bound to surrounding soft tissues and are impacted less by effects of reduced tissue clearance 2° vasoconstriction
 - Unlike other vasoconstrictor agents, Adr can enhance quality of analgesia (independent of vasoconstrictor activity) by (i) directly increasing neuronal uptake of LA, and (ii) via a direct α -adrenergic mechanism
 - Adr has issues with CVS toxicity (esp in patients with CV disease) – (i) Cause systemic HTN and tachycardia, (ii) Issues of arrhythmogenic effects when used with VAs (esp halothane), and (iii) Issues of potentiating CVS toxicity with LAs (esp cocaine)
 - (2) Phenylephrine (α_1 agonist)
 - (3) Felypressin (synthetic derivative of vasopressin without ADH effect)

Combination of Local Anaesthetic Drugs:

- LA drugs can be combined to produce a rapid onset (Ie. using lignocaine) and prolonged duration (Ie. using bupivacaine)
- Note, however, that LA toxicity of combining LA drugs are ADDITIVE (like MAC and VAs) rather than synergistic (Ie. 50% toxic dose of one LA drug and 50% toxic dose of another LA drug will have 100% toxic effect of either drug)

(d) *To describe the pharmacokinetics of local anaesthetics and potential alterations with physiological and pathological disturbance.*

Plasma Concentration of Local Anaesthetic Drugs:

- Plasma [LA] achieved following injection of a LA is determined by its:
 - o (1) Rate of absorption from injection site into systemic circulation
 - o (2) Rate of tissue redistribution
 - o (3) Rate of clearance via metabolism and excretion

Absorption of Local Anaesthetic Drugs:

- Rate of LA drug absorption from the injection site into the systemic circulation are influenced by factors that determine tissue blood flow at the injection site:
 - o (1) Site of injection – Highly vascularised tissue → ↑ blood flow and ↑ systemic absorption

IV > Trachea & mucosal membrane > Intercostal > Paracervical > Caudal > Paravertebral > Epidural > Brachial plexus > Spinal > S/C > Intact skin

- o (2) Use of vasoconstrictor agents (Eg. Adr) – Vasoconstriction → ↓ blood flow and ↓ systemic absorption
- o (3) LA drug factors
 - Dose applied – ↑ dose will lead to ↑ systemic absorption
 - Intrinsic vasodilator activity – ↑ blood flow and ↑ systemic absorption
 - Lipid solubility – ↑ lipid solubility → ↑ systemic absorption
 - pKa of LA/Tissue pH – ↑ fraction unionised → ↑ systemic absorption
 - Protein binding – LA highly-bound to tissue have ↓ systemic absorption

Distribution of Local Anaesthetic Drugs:

- Redistribution of LA in the body depends on organ uptake, which is determined by:
 - o (1) Tissue perfusion (C.O. and regional blood flows) – LA is the systemic circulation distributes first to highly perfused organs (lungs, brain, heart, liver, kidneys) → then to less well-perfused organs (incl muscle, fat, GIT)
 - o (2) Tissue/blood partition coefficient – Poor plasma-protein binding by LA and/or high lipid solubility of LA → ↑ redistribution to tissues; opposite is true
 - o (3) Tissue mass – Muscles are the largest reservoir for LA due to its high mass
- Specialised areas of LA redistribution:
 - o “First-pass pulmonary extraction” of LA – Lungs can extract significant amount of LA (esp lignocaine, bupivacaine, prilocaine) from the venous circulation, thus limiting the amount of LA reaching the systemic circulation → Thus, arterial injections are associated with less systemic toxicity than IVI!
 - o Placental transfer of LA is determined by – (i) Protein binding of LA (↑ protein binding (Eg. bupivacaine cf. lignocaine) means ↓ transfer to foetus), (ii) LA type (ester LA are rapidly metabolised so ↓ transfer to foetus), and (iii) Foetal pH (foetal acidosis (Ie. prolonged labour) → ↑ LA ion trapping)
- Plasma protein binding of LA:
 - o LA bind to α1 acid glycoprotein (A1AGP) with high affinity, BUT bind albumin at a larger quantity due to its relative abundance in plasma
 - o Ester LAs are minimally bound, while amide LAs are more extensively bound (bupivacaine > ropivacaine > lignocaine > prilocaine)
 - o Degree of protein binding is INVERSELY related to free fraction of drug in plasma (Ie. for redistribution/systemic effects)

Clearance of Local Anaesthetic Drugs: Metabolism and Elimination

- Metabolism of LA:

○ (1) Amide LA

- Hepatic metabolism by CYP450 MEOs (I.e. convert amide base to aminocarboxylic acid and cycline aniline derivatives, then further processing via hydroxylation, N-dealkylation, conjugations, Etc.) into inactive water-soluble metabolites that are excreted in urine
- Slow and complex hepatic metabolism → Leads to more sustained plasma [LA] and ↑ risk of systemic toxicity

(Fastest) Prilocaine > Lignocaine > Mepivacaine > Etidocaine > Ropivacaine > Bupivacaine (Slowest)

- Metabolism impaired by (i) Liver disease (Eg. cirrhosis) and/or (ii) Decreased HBF (Eg. GA, CCF, propranolol, cimetidine) → Accumulation of LA in plasma and risk of systemic toxicity

○ (2) Ester LA

- Rapid hydrolysis by plasma cholinesterase (and lesser extent liver cholinesterase) into inactive water-soluble metabolites that are excreted in urine

EXCEPT cocaine – Apart from hydrolysis by plasma esterases, it also undergoes EXTENSIVE hepatic metabolism (via N-methylation and hydrolysis by liver esterases) → water-soluble metabolites excreted in urine

- Fast and efficient metabolism → Lower risk of LA accumulation in plasma thus ↓ risk of systemic toxicity

(Fastest) Chlorprocaine > Procaine > Tetracaine (Slowest)

- Metabolism by plasma cholinesterase is impaired by same factors that retard metabolism of SCh → Result in ↑ risk of LA accumulation in plasma and systemic toxicity:
 - (i) Qualitative ↓ enzyme activity (genetically-aberrant PC – atypical/silent/fluoride-resistant; drugs – AChEi, chemo agents, SCh, metoclopramide, OCP, Li, Etc.; disease states – CCF, renal failure, TTX; hypothermia; pregnancy)
 - (ii) Quantitative ↓ in enzyme levels (liver disease, malnutrition)
- Note – Metabolites of ester LAs (esp procaine, benzocaine) include “Para-aminobenzoic acid” → Implicated as an antigen in allergic reactions

- Elimination of LA:

- LA drugs are very poorly water-soluble → Thus, limits renal elimination of unchanged LA drug to < 5% (EXCEPT cocaine, which is ~10% excreted in urine unchanged)
- Metabolites of LA drugs, however, are highly water-soluble → Excreted renally

(f) *To explain the factors that determine the clinical effects of local anaesthetic drugs.*

Potency of LA Drugs:

- Determined mainly by the “lipid solubility of the LA drug” – This is ↑ by:
 - o (i) Adding more C-atoms (I.e. larger molecular size)
 - o (ii) Adding large alkyl groups to tertiary amine or aromatic ring (Eg. bupivacaine vs mepivacaine)
 - o (iii) Halogenation of the aromatic ring (Eg. chloroprocaine vs procaine)
 - o (iv) Presence of an ester linkage (Eg. procaine vs procainamide)
 - o (v) Increasing the unionised fraction (I.e. using low pKa drug or alkalinisation the environment)
- Other determinants include:
 - o (i) Intrinsic vasodilator activity of LA agent – ↑ regional blood flow 2° to vasodilation leads to ↑ systemic absorption → ↓ potency
 - o (ii) Presence of vasoconstrictor agent – ↓ regional blood flow 2° to vasoconstriction leads to ↓ systemic absorption → ↑ potency
 - o (iii) Protein binding – Agents with high protein binding will have ↑ potency (as more remain at injection site and less redistributed to peripheral tissues)
 - o (iv) Clearance – LA drugs that are more slowly metabolised and eliminated (Eg bupivacaine) have ↑ potency

Measure of potency: “Minimum concentration (Cm)”

- Defined as the minimum concentration of LA needed to produce conduction blockade of nerve impulses (analogous to MAC and VAs)
- Factors influencing Cm:
 - o (1) Peripheral nerve factors
 - Diameter/myelination – Larger nerve and myelination requires a higher [LA] → ↑ Cm
 - Fibre type – Different fibre types have different sensitivities to LA (ANS fibres > sensory fibres > motor fibres in terms of LA sensitivity) → Less sensitive nerve fibres will have ↑ Cm
 - Nerve activity – Frequent nerve stimulation causes ↑ frequency-dependent conduction blockade → ↓ Cm
 - o (2) LA type – More lipid-soluble agent → ↑ potency thus ↓ Cm
 - o (3) Tissue pH – Alkali environment → ↑ fraction unionised → Thus ↓ Cm
 - o (4) Electrolytes – Hypokalaemia and hypocalcaemia antagonises conduction blockade → thus ↓ Cm
- Nb. Cm is NOT affected by route of LA administration (I.e. LA given as part of epidural and spinal anaesthesia have similar Cm, despite needing less dose for the latter)

Onset of Action of LA Drugs:

- Determined mainly by (i) pKa of the LA and (ii) pH of the environment the LA is in
 - o These factors dictate the relative concentration of lipid-soluble unionised form (B) and water-soluble ionised form (BH⁺) that exists at equilibrium

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

- o LA are weak bases (pKa 7.6-8.9) that exists predominantly in its water-soluble ionised form (I.e. >50% of LA carry +ve charge at tertiary amine group) at physiological pH
- o Fraction of unionised drug is ↑ with either a (i) low pKa LA (Eg. lignocaine) or (ii) high pH environment (Eg. alkalinisation) → Allows more LA to pass through excitable cell membrane → Faster onset of action LA

- Conversely, 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
- Within the axoplasm, the environment is acidic → Favours ↑ fraction of ionised drug which then binds avidly to the α -subunits of the VG Na⁺ channel from inside the cell
- Other factors include:
 - (i) Site of LA injection (Ie. rapid onset with topical anaesthesia at mucosal membranes due to weak barrier to LA; slower onset with epidural anaesthesia due to longer diffusion to nerve tissue)
 - (ii) Lipid solubility of LA – More lipid-soluble agents have a faster onset
 - (iii) Dose of LA administered – ↑ dose given leads to faster onset

Duration of Action of LA Drugs:

- Determined mainly by “lipid solubility of the LA drug” – ↑ lipid solubility means:
 - More tissue protein binding → ↓ clearance from injection site by regional blood flow
 - More plasma protein binding → ↓ redistribution to other tissues, and ↓ clearance by liver/kidneys/plasma enzymes
- Other factors:
 - (i) Dose of LA administered – ↑ dose given leads to ↑ duration of action
 - (ii) Intrinsic vasodilator activity of LA agent – ↑ regional blood flow 2° to vasodilation leads to ↑ systemic absorption → ↓ duration of action
 - (iii) Presence of vasoconstrictor agent – ↓ regional blood flow 2° to vasoconstriction leads to ↓ systemic absorption → ↑ duration of action
 - (iv) Use of liposomal delivery systems or LMWT dextrans → ↑ duration of action
 - (v) Clearance – LA drugs that are more slowly metabolised and eliminated (Eg bupivacaine) have ↑ duration of action

(e) *To describe the pharmacodynamics of the local anaesthetics with particular reference to the neuronal, central nervous system and cardiovascular effects.*

(h) *To describe local anaesthetic toxicity. To describe its prevention and management.*

Side-effects of LA drugs can be either due to – (i) Allergic reactions or (ii) Systemic toxicity

Allergic Reactions to LA Drugs:

- Allergic reactions to LA are rare (cf. systemic toxicity) and commonly “misdiagnosed”
- They occur:
 - o (i) More commonly with ester LAs due to an antigenic metabolite (para-aminobenzoic acid; PABA) produced only from metabolism of ester LAs (esp procaine and benzocaine)
 - o (ii) With both ester and amide LA preparations due to the presence of preservatives related to PABA (esp methylparaben)

Note: Cross-sensitivity to LA drugs

- Can occur between LA drugs that produce PABA metabolite (I.e. other ester LAs)
- Do NOT occur between different LA classes, provided that the preparation is preservative-free (I.e. no allergy risk to preservative-free amide LA solution in a patient allergic to ester LAs)

- Features of LA-induced allergy reaction:
 - o Symptoms and signs include – Rash, urticaria, laryngeal oedema +/- hypotension and bronchospasm
 - o Confirmed with intradermal test (inject preservative-free LA solution)
- Treatment of LA-induced allergy reaction:
 - o (i) Stop injecting LA drug
 - o (ii) Treat as allergic reaction/anaphylaxis – Steroids, H1/H2RBs, fluids and adrenaline in severe cases

Systemic Toxicity to LA Drugs:

Overview of systemic toxicity:

- Systemic LA toxicity is caused by excessive plasma [LA] that can occur due to:
 - o (1) Accidental direct IV injection of LA during a regional technique (common)
 - o (2) Excessive absorption of LA from injection site (less common; see above for factors for rate of LA drug absorption from the injection site)
- Plasma [LA] at which systemic LA toxicity occurs:

LA agent	Plasma [LA] causing toxicity
Lignocaine	> 5 mcg/mL
Prilocaine	> 5 mcg/mL
Procaine	> 5 mcg/mL
Ropivacaine	> 4 mcg/mL
Bupivacaine	> 3 mcg/mL
Levobupivacaine	> 3 mcg/mL
Cocaine	> 0.5 mcg/mL

- Systemic LA toxicity manifests with:
 - o Features of CNS toxicity occurring first – CNS is very vulnerable to LA toxicity because LA drugs can easily penetrate the BBB → Thus, features of CNS toxicity are recognised as premonitory signs of systemic LA toxicity in an awake patient
 - o Features of CVS toxicity occurring late – CVS is more resistant to LA toxicity (I.e. requires 3x higher plasma concentration to produce CVS toxicity than to produce

seizures) → Thus, features of CVS toxicity are recognised as signs of systemic toxicity during GA when CNS toxicities are masked (or missed in an awake patient)

CNS:CVS toxicity ratio:

- Dose ratio from onset of CNS symptoms (reversible and treatable) to onset of CVS symptoms (life-threatening and refractory to treatment) → Provides a therapeutic window and a measure of safety
- I.e. lignocaine 7; ropivacaine 4; bupivacaine 3

Features of systemic lignocaine toxicity:

Plasma conc.	Effect
1-5 mcg/mL	Analgesic and antiarrhythmic effects
5-10 mcg/mL	- Circumoral numbness, tinnitus, dysarthria, skeletal muscle twitching - Hypotension, myocardial depression
10-15 mcg/mL	Seizures and LOC
15-25 mcg/mL	Respiratory depression/apnoea and coma
> 25 mcg/mL	CVS collapse (cardiac arrhythmias, asystole, profound hypotension)

CNS and Neurotoxicity due to LA drugs:

- CNS toxicity due to LA drugs:
 - CNS toxicity occurs early – CNS is very vulnerable to LA toxicity because LA drugs can easily penetrate the BBB → Thus, features of CNS toxicity are recognised as premonitory signs of systemic LA toxicity in an awake patient
 - Features of CNS toxicity follow the following pattern:
 - Non-specific symptoms first – Numbness of the tongue and circumoral tissues, and metallic taste (due to high tissue vascularity of the tongue/lips)
 - Then excitatory symptoms (due to depression of inhibitory cortical interneurons):
 - Initially confusion, visual disturbance (diplopia, difficulty focusing), restlessness/agitation, dizziness, vertigo and tinnitus
 - Later tremor and twitching of face and extremities → soon heralds onset of GTC seizures
 - Then finally depressive symptoms (due to central neuronal depression)
 - Slurred speech and drowsiness initially
 - Finally leading to LOC/coma and respiratory depression/apnoea

Risk factors for CNS toxicity and seizures:

- (1) Potent and lipid-soluble LA drugs – These agents (Eg. bupivacaine and ropivacaine) are more likely to produce CNS toxicity at a lower plasma [LA] (cf. lignocaine)
- (2) ↑ PaCO₂ – Reduces threshold for CNS toxicity due to ↑ CBF (and LA delivery)
- (3) ↑ K⁺ – Reduces threshold for CNS toxicity due to ↑ neuronal depolarisation
- (4) Drugs – Antiarrhythmic drugs (Eg. mexiletine) lowers the threshold for CNS toxicity; CNS depressants (Eg. Bz, STP) increases the threshold for CNS toxicity
- (5) Pregnancy – Lowers threshold for CNS toxicity
- (6) Neonates/foetus – ↑ risk of CNS toxicity due to less mature BBB, ↓ protein binding (due to ↓ A1AGP), ↓ LA metabolism (due to immature liver), ↑ acidosis

- Neurotoxicity due to LA drug placement as part of neuraxial block:

Lignocaine (and likely other LAs) are known to be directly neurotoxic to sensory neurons – Thought to be caused by increases in IC Ca^{2+} levels

○ (1) Transient Neurologic Symptoms

- Moderate-severe burning pain in lower back, buttocks and posterior thighs that occur within 6-36 hrs after complete recovery from SAB
- Potentially caused by ?radicular irritation

Risk factors for TNS:

- (i) Significantly high incidence if lignocaine used (cf. other LAs)
- (ii) LA used with ADR (ADR decreases nerve blood supply causing nerve ischaemia; also increase exposure to LA nerve toxicity)
- (iii) Patient positioning (esp lithotomy position)
- (iv) Outpatient status (esp early ambulation)
- (v) Obesity

- Treated with trigger point injections and NSAIDs (and opioids, if severe). Full recovery within 1-7 days

○ (2) Cauda Equina Syndrome

- Diffuse injury of lumbo-sacral plexus resulting in (i) sensory anaesthesia, (ii) bowel/bladder sphincter dysfunction, and (iii) paraplegia

Risk factors for CES:

- (i) LA used in continuous spinal anaesthesia via small-bore catheters → This causes concentration of LA on stretched nerves 2° to patient positioning (esp lithotomy position) (Nb. CES can also occur with single shot spinal anaesthesia!)
- (ii) Type of LA used – Mainly with lignocaine and tetracaine

○ (3) Anterior spinal artery syndrome

- Lower extremity paresis with variable sensory deficit
- Due to thrombosis, spasm or vasoconstriction (2° to ADR) of the anterior spinal artery; can occur also due to systemic hypotension

CVS Toxicity due to LA drugs:

- Features of CVS toxicity occur late – CVS is more resistant to LA toxicity (I.e. requires 3x higher plasma [LA] to produce CVS toxicity than to produce seizures) → Thus, features of CVS toxicity are recognised as signs of systemic toxicity during GA when CNS toxicities are masked (or missed in an awake patient)
- Features of CVS toxicity include:
 - Initially transient CVS excitation (tachycardia and HTN)
 - Followed by CVS depression (bradycardia, AV heart block, profound hypotension → progressing to ventricular tachyarrhythmias (VT/VF), asystole, cardiac arrest and circulatory collapse)

Risk factors that ↓ threshold to LA-induced CVS toxicity:

- (1) Pregnancy
- (2) Foetus/neonates (↑ risk of CVS toxicity due to ↑HR, ↓ protein binding (due to ↓ A1AGP), ↓ LA metabolism (due to immature liver), ↑ acidosis)
- (3) Drugs (Adrenaline, beta-blockers, digoxin, CCBs)
- (4) ↓ PaO_2
- (5) ↑ PaCO_2
- (6) Acidosis

- Mechanism of CVS toxicity:

- LAs exert CVS effects via – (i) Direct cardiac muscle effect → depresses V_{MAX} (maximal depolarisation rate of cardiac AP) 2° antagonism of cardiac VG Na^+ channels, and (ii) Inhibition of ANS
 - The effect on the CVS is:
 - (i) ↓ cardiac conduction velocity, ↓ refractory period duration and ↓ automaticity (spontaneous phase 4 depolarisation) → prolonged PR interval and QRS complex
 - (ii) ↓ myocardial contractility (direct –ve inotropy)
 - (iii) Arteriolar vasodilation due to VSM relaxation (except for cocaine)
 - LA-selective CVS toxicity:
 - Accidental IVI of bupivacaine results in severe CVS toxicity that is refractory to resuscitation (I.e. prolonged resuscitation, high vasopressors needs)
- Bupivacaine (most CVS-toxic) > Levobupivacaine > Ropivacaine > Lignocaine
- Mechanism:
 - Cardiotoxic LAs (esp R-isomer of bupivacaine) are highly lipid-soluble and protein-bound → Associate rapidly with cardiac VG Na^+ channel during systole and dissociate very slowly from them during diastole → Causes persistent V_{MAX} depression and risk of re-entrant arrhythmias
 - Less cardiotoxic LAs (esp lignocaine and ropivacaine) are less lipid-soluble and protein-bound → Bind to the channel with less affinity during systole, and readily dissociate away from them during diastole
 - ↑ HR predisposes to further CVS toxicity due to frequency-dependent channel blockade
 - At high doses, QTc is prolonged 2° VG- Ca^{2+} and K^+ channel blockade

Methaemoglobinaemia due to LA Drugs:

- Specific LAs (esp prilocaine and benzocaine) favours the [O] of Hb to Met-Hb (and causing methaemoglobinaemia) due to the production of an O-toluidine metabolite
- Consequence of Met-Hb – Normal adult Hb loses its transport function (I.e. cannot bind O_2/CO_2) and central cyanosis ensues when [Met-Hb] > 15% of total Hb (normally it is < 1% total Hb)
- Risk of methaemoglobinaemia in association with LA use is ↑ with:
 - (i) Use of specific LAs (esp prilocaine, benzocaine, lignocaine)
 - (ii) Concurrent use of drugs that predispose to methaemoglobinaemia (Eg. GTN, SNP, phenytoin, sulphonamides)
 - (iii) Preexisting congenital or idiopathic methaemoglobinaemia
 - (iv) Children < 3/12 old (due to immature RBC met-Hb reductase pathway)
- Diagnosis of methaemoglobinaemia – Often suspected when there is discrepancy of measured and calculated SaO_2 → Confirmed by qualitative measurements of Met-Hb by co-oximetry
- Treatment of methaemoglobinaemia:
 - IV methylene blue 1-2 mg/kg (over 5 mins) is a reducing agent that restores normal adult Hb within 20-60 mins
 - It has a short $t_{1/2}$ → Risk of clearing from body before full reduction of all met-Hb (esp when lipophilic LAs (Eg. benzocaine) are used and cleared slowly from fat stores)

Respiratory toxicity due to LA Drugs:

- Respiratory depression → apnoea due to LAs occur because of:
 - (i) Inadvertent phrenic/intercostals nerve paralysis during regional anaesthesia
 - (ii) Depression of medullary respiratory centre (often 2° excessive spinal anaesthesia) → Due to ischaemia depression caused by profound hypotension

and ↓ CBF (rather than direct effect of LA in ventricular CSF acting on respiratory centre)

- Lignocaine specifically can cause:
 - (i) Ventilatory depression response to arterial hypoxaemia (issue in patients who are dependent on hypoxic drive, such as CO₂ retainers)
 - (ii) Bronchospasms (esp in those with reactive airways)

Musculoskeletal toxicity due to LA Drugs:

- LAs are myotoxic (esp bupivacaine > lignocaine > procaine) when directly injected into skeletal muscle → Causes myonecrosis (esp when steroids or adrenaline are used concurrently)
- Muscle regeneration occurs in 4 weeks

Management of Systemic LA Toxicity:

- (1) Treatment should commence when there is evidence of systemic LA toxicity (sudden altered mental state, severe agitation, LOC +/- GTC, or CVS collapse)
- (2) Immediately stop injecting LA
- (3) Airway management and aggressive ventilation:
 - Consider intubation to protect against aspiration
 - Adequate ventilation to prevent and treat arterial hypoxaemia, hypercapnoea and metabolic acidosis (which exaggerate LA-induced CVS and CNS toxicity)
- (4) In event of seizures → Consider seizure suppression with IV STP, Bz or propofol
- (5) In event of circulatory arrest
 - Immediate CPR → ACLS
 - Treat arrhythmias with Amiodarone (alt. bretylium) → Do NOT use lignocaine!
 - Treat hypotension with vasopressors (vasopressin preferred over Adr and NAd)
 - Treat bradycardia with atropine/isoprenaline (+/- cardiac pacing)
 - Institute “lipid rescue therapy” (20% intralipid):
 - Bolus 1.5 mL/kg over 1 min and infuse at 15 mL/kg/hr. After 5 mins, if CVS stability not restored or deteriorates further, give maximum 2x further repeat boluses (5 mins apart) at same dose AND double infusion rate to 30 mL/kg/hr. Continue infusion until patient stabilised or maximum dose given (12 mL/kg)
 - Mechanism – Lipids draw LA (esp highly lipid soluble LAs) from binding sites in the heart back into plasma → ↑ threshold for LA toxic dose
 - Note – Propofol should NOT be used for lipid rescue therapy as (i) lipid content is too low for an effect, and (ii) CVS depression → CVS collapse
 - Consider cardiopulmonary bypass if all fails
- (6) In absence of circulatory arrest
 - Treat hypotension, bradycardia and tachyarrhythmias as above
 - Consider lipid rescue therapy
- (7) Prolonged monitoring and resuscitation required – This is because CVS toxicity persists for > 1 hr (due to long duration of action of highly lipid soluble LAs)!

Prevention of Systemic LA Toxicity:

- (1) Close monitoring for features of systemic LA toxicity
 - Monitor with ECG, NIBP and SaO₂
 - Vigilance for symptoms → CNS symptoms are subtle or absent, and CVS signs are often a late feature of toxicity → Institute prompt therapy
 - Patient should be monitored for > 30 mins post-LA injection as toxicity can manifest some time after injection (due to delayed rise in plasma [LA] from systemic absorption)
- (2) Test dose of LA – Slow or fractionated administration of LA to detect features of systemic toxicity from accidental IV injection

- (3) Use of pharmacologic marker (Eg. adrenaline) to assess for accidental IV injection
- (4) Aspirating syringe prior to injection to prevent IV injection
- (5) Minimise total LA dose used (esp at injection sites of ↑ vascularity and patients with risk factors that ↓ the threshold for CNS/ CVS toxicity)
- (6) Limit bupivacaine [] to 0.5% to minimise CVS toxicity

Aside: Clinical Uses of Local Anaesthetic Drugs

Regional Anaesthesia:

- (1) Topical anaesthesia:
 - Involves placement of LA on mucous membrane (I.e. of nose, mouth, tracheobronchial tree, Etc.) or on skin → Used for:
 - (i) ENT surgery (cocaine spray is favoured due to ↓ bleeding 2° to its vasoconstrictor effect)
 - (ii) ↓ stimulation of DL or FOB when intubating (with nebulised lignocaine)
 - (iii) ↓ bronchial reactivity/bronchospasm (with nebulised lignocaine)
 - (iv) Anaesthetise skin with EMLA to permit vascular line insertion (Eg. IVC, arterial line), cautery of skin lesions, circumcision, skin-graft harvest

Issues:

- (i) Nebulised lignocaine can precipitate bronchospasm in patients with reactive airways disease
- (ii) Risk of systemic toxicity as plasma [LA] achieved is similar to that of IVI (due to ↑ vascularity of mucosal membranes)
- (iii) EMLA carries ↑ risk of methaemoglobinaemia (esp in certain patients)

- (2) Local infiltration:
 - Involves extravascular placement of LA in the area to be anaesthetised → Used to (i) Permit vascular line insertion (Eg. arterial line, CVC), and (ii) Infiltrate operative site for analgesia
 - LA used – Lignocaine commonly used (alt. ropivacaine and bupivacaine) → Duration ↑ 2x using Adrenaline 1:200,000

Note: Adrenaline should be avoided in tissues supplied by end-arteries (digits, ears, nose, penis) due to distal ischaemia and risk of gangrene

- (3) Peripheral nerve block anaesthesia:
 - Involves injection of LA into tissue surrounding peripheral nerve/nerve plexuses (Eg. femoral nerve block, brachial plexus block)
 - LA used – Lignocaine (+/- Adr), Bupivacaine (+/- Adr), Ropivacaine, Levobupivacaine
 - Pattern of anaesthesia:
 - Develops proximally then spreads distally at onset (and in the reverse order with recovery):
 - Peripheral nerve fibres consist of (i) an outer surface (mantle) → supplies proximal structures, and (ii) a central “core” → supplies distal structures
 - LA diffuses from outer surface (mantle) of peripheral nerve towards its centre (core) along its [] gradient → Thus nerve mantle is anaesthetised first (and anaesthesia develops proximally), then finally the core (and anaesthesia spreads distally)
 - Pattern of block (sensory, motor, autonomic) depends on:
 - (i) Anatomical location of nerve fibre within mixed peripheral nerve (I.e. paralysis occurs early if motor nerve fibre is more peripheral than the sensory fibre in a peripheral nerve)
 - (ii) Nerve sensitivity to LA (which is determined by nerve fibre size and myelination; See above) → Small sensory and ANS fibres are blocked first then large proprioceptive and motor fibres
- (4) IV regional anaesthesia (Bier Block):

- Involves IV injection of LA into an extremity that is isolated from the rest of the systemic circulation by a tourniquet. Results in:
 - Rapid onset of anaesthesia and muscle relaxation in an isolated extremity due to accumulation of LA in the isolated extremity → Acts on nerve endings and trunks
 - Prompt reversal of anaesthesia and muscle relaxation when tourniquet is released → Blood flow dilutes LA in extremity

Note: Duration of effect is determined solely by tourniquet inflation (and NOT the type of LA used)!

- LA used for IVRA:
 - (i) Lignocaine (commonly used)
 - (ii) Prilocaine (similar effect as lignocaine but ↓ risk of systemic toxicity due to lower plasma [LA] observed with tourniquet release; Met-Hb not an issue as plasma [LA] are below level needed to cause cyanosis)
 - (iii) Mepivacaine (superior anaesthetic effect cf. lignocaine)

Note: The following LAs should NOT be used with IVRA

- Bupivacaine and Ropivacaine → Risk of cardiotoxicity
- Chloroprocaine → Risk of thrombophlebitis

- (5) Epidural anaesthesia:
 - Involves injecting LA into epidural/caudal space to causes anaesthesia as follows:
 - (i) LA diffuses across dura → Act directly on nerve roots and spinal cord (similar to spinal anaesthesia)
 - (ii) LA diffuses into paravertebral space through intervertebral foramina → Effect of multiple paravertebral nerve blocks
 - LA used – Lignocaine, Bupivacaine, Levobupivacaine, Ropivacaine
 - Pattern of anaesthesia:
 - Delay in anaesthesia (15-30 mins) due to slow diffusion process of LA, and larger doses of LA required (cf. SAB) → ↑ systemic absorption and risk of systemic LA toxicity
 - Zone of differential blockade – Sensory blockade level usually 4 levels above motor blockade level (cf. 2 levels with SAB), and no SNS blockade level (unlike SAB)
 - Epidural opioids can be given concurrently → Synergistic effect with LA
 - Adrenaline (as part of LA solution) ↓ systemic LA absorption by 33% BUT does not prolong effect of LA in epidural anaesthesia → In fact, it causes ↓ BP 2° peripheral vasodilation (through β effect) despite ↑ ino- and chronotropy!
- (6) Spinal anaesthesia:
 - Involves injection of LA into CSF within lumbar subarachnoid space → acts on superficial layers of spinal cord and nerve roots to produce sensory anaesthesia and skeletal muscle relaxation
 - LA used – Lignocaine, Bupivacaine, Levobupivacaine, Ropivacaine, or Tetracaine can be given

Note:

- LAs for spinal anaesthesia should be preservative-free to prevent neurotoxicity (esp arachnoiditis risk)
- Chloroprocaine should be avoided → Due to presence of preservatives and direct neurotoxicity by LA
- Lignocaine dose should be limited to 60 mg due to risk of TNS

○ Pattern of anaesthesia:

- Anaesthetic effect determined by total dose of LA given (rather than volume or [] of LA) → Dose is determined by:
 - (i) Height of patient (determines volume of SA space)
 - (ii) Segmental level of anaesthesia desired
 - (iii) Duration of anaesthesia desired
- Distribution of anaesthesia (I.e. spread of LA) is determined by the specific gravity of the LA solution:
 - Hyperbaric solution – Addition of glucose to LA increases the SG above CSF fluid
 - Hypobaric solution – Addition of distilled water lowers the SG of LA solution below CSF
- Zones of differential blockade (caused by distribution of LA [] gradient within the CSF from the site of injection, and the different nerve fibre sensitivities to LA) → SNS blockade level occurs 2 segments above sensory blockade level, and motor blockade level occurs 2 segments below sensory blockade level
- Duration of anaesthesia dependent on systemic absorption of drug and metabolism in plasma/liver (as there are no cholinesterases in CSF!)
- Risk of systemic toxicity is low because – (i) Low LA doses are given, and (ii) Systemic absorption from CSF is very low

Issues:

- SNS blockade
 - Hypotension (33%)
 - Caused principally by venodilation → ↓ venous return and subsequent ↓ CO and BP (esp if volume-depleted)
 - Arteriolar vasodilation has a minor effect on ↓ BP because – (i) Denervated arterioles retain intrinsic tone and do NOT maximally dilate, and (ii) Reflexive arteriolar vasoconstriction occur in vascular beds with intact SNS response
 - Bradycardia (13%)
 - Caused by – (i) Blockade of T1-T4 preganglionic cardiac accelerator fibres, and (ii) Bezold-Jarisch reflex (↓ VR 2° venodilation → ↓ stimulation of right atrial stretch receptors → reflexive slowing of HR)
 - Cardiac arrest (in severe cases) → Tends to be refractory to resuscitation as the SNS blockade (i) Blunts the neuroendocrine response to stress, and (ii) ↓ the effective circulating blood volume

Note: Sequelae of SNS blockade more likely if – (i) Sensory level > T5, (ii) Baseline SBP < 120 mmHg, (iii) Baseline HR < 60 bpm, (iv) Prolonged PR interval, (v) Use of β-blockers/CCB

- Apnoea
 - Caused by ischaemic paralysis of medullary ventilatory centres 2° to profound hypotension (and ↓ CBF) as a consequence of a profound SAB (and NOT due to direct effect of LA in ventricular CSF acting on the medulla!)
 - Rarely due to phrenic nerve or intercostals nerve paralysis

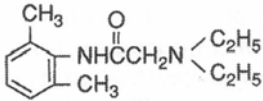
Non-regional anaesthesia uses of LA drugs:

- (1) Prevent/treat cardiac tachyarrhythmias
 - IV lignocaine at low doses is useful in treating certain ventricular tachyarrhythmias (as a class 1b agent)
- (2) Supplementing a GA

- IV infusions of lignocaine or procaine provide intense analgesia (ideal for post-op pain and ↓ opioid usage) → BUT limited by small margin of safety with IVI of LAs and ↑ risk of systemic toxicity
 - IV lignocaine is MAC-sparing (↓ VA use by 40%)
 - IV lignocaine can be used to ↓ stimulation due to intubation/extubation → Suppress haemodynamic response and coughing, ↓ elevations in ICP, and prevent bronchospasms
- (3) Treat grand-mal seizures
 - Low doses of LAs (Eg. lignocaine) can depress hyperexcitable cortical neurons
- (4) Anti-inflammatory and anti-bacterial effects
 - Epidural and spinal anaesthesia can modulate inflammatory responses (due to disruption of inflammatory mediator signalling and PMNL inhibition 2° to antagonism of GPRC) → ↓ perioperative inflammatory injury (Ie. postoperative pain, SIRS, MOF, ARDS, hypercoagulable states) BUT can also ↓ wound healing and ↑ risk of infection
 - LAs also possess antibacterial effects (tetracaine > bupivacaine > lignocaine)
- (5) Bronchodilation
 - Inhaled lignocaine and ropivacaine can ↓ bronchial reactivity and prevent bronchospasms via a topical anaesthetic effect

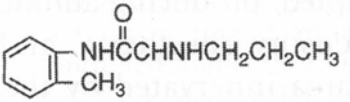
(g) *To compare the pharmacology of the local anaesthetics with particular reference to lignocaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine, cocaine and procaine.*

Lignocaine:

Type and structure	Amide LA – Tertiary amine derivative of diethylaminoacetic acid Mwt. 234.3 g/mol 
Preparation	Lignocaine HCl as a clear colourless solution (0.5%, 1%, 1.5%, 2%) +/- adrenaline (1 in 200k); 2% gel (+/- chlorhexidine); 4% aqueous solution for topical applications; 5% ointment; 10% spray
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient 2.9 70% protein-bound (esp to A1AGP) pKa 7.8 (25% unionised at phgyl pH) Vd 0.7-1.5 L/kg
Metabolism and excretion	- Clearance 7-11 mL/min/kg; $t_{1/2\beta}$ 90-110 mins - Cleared mainly via hepatic metabolism – N-dealkylation to acetaldehyde and monoethylglycinexylidide (80% activity as parent drug and longer $t_{1/2\beta}$ → explains prolonged antiarrhythmic activity after cessation of lignocaine). Latter metabolite undergoes hydrolysis to xylidide (10% activity as parent), which is mainly excreted in urine (75%) - Minimally cleared renally (< 10% excreted unchanged in urine) - Nb. Clearance ↓ with liver disease or ↓ HBF (Eg. CCF, β -blockers, GA)
Pharmacodynamics	
Dosing and effects	- Potency: + - Max. dose: 3 mg/kg (7 mg/kg with Adr); 300 mg as single bolus - Toxic plasma [LA]: > 5 μ g/mL - Rapid onset (2 mins) with intermediate duration (0.75-2 hrs)
Intrinsic vasodilator activity at low []	Prilocaine > <u>lignocaine</u> > bupivacaine > mepivacaine > ropivacaine * Nb. At high [] → Vasoconstrictor effect
Clinical uses	(1) Regional anaesthesia (topical, infiltration, IVRA, PNS, SAB, EDB) (2) Antiarrhythmic agent (Class 1b) → Low IV doses used to treat/prevent ventricular tachyarrhythmias (3) Supplement GA as IVI – (i) MAC sparing (40%), (ii) ↓ stimulation of intubation/extubation (↓ haemodynamic response, attenuate ↑ ICP, prevents coughing and bronchospasm), (iii) Analgesia (↓ post-op pain and opioids demands; also ↓ pain with propofol injection) (4) Potent analgesia when given as IVI (5) Treat seizures – Low doses depress cortical neuron excitation (6) Anaesthetise airway using nebulised form → Permit instrumentation (Eg. DL/FOB) or treat/prevent bronchospasms (via bronchodilatory effect)
Issues	(1) Ventilatory depression response to arterial hypoxaemia (issue in patients who are dependent on hypoxic drive, such as CO ₂ retainers) (2) Bronchospasms (esp in those with reactive airways) (3) Neurotoxicity (due to ↑ in IC [Ca ²⁺]) – During spinal anaesthesia, dose limited to 60 mg to prevent TNS; risk of CES esp when continuous infusions via small-bore catheters (4) ↑ crosses placenta due to ↓ protein binding (esp during foetal acidosis) cf. bupivacaine

	(5) ↑ systemic toxicity with liver disease or ↓ HBF (Eg. CCF, GA) (6) Allergies rare (often due to preservatives)
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Prilocaine:

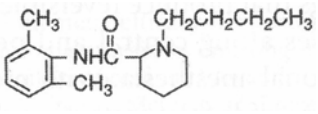
Type and structure	Amide LA – Secondary amine derivative of toluidine Mwt. 220.3 g/mol 
Preparation	Prilocaine HCl as clear colourless solution (0.5%, 1%, 2%, 4%); 3% with felypressin for dental use
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient 141 55% protein-bound (esp to A1AGP) pKa 7.8 (24% unionised at phgl pH) Vd 1.5-3.0 L/kg
Metabolism and excretion	- Clearance ?; $t_{1/2\beta}$ 96 mins - Cleared mainly by hepatic metabolism (but also in kidneys and lung) – Metabolised to ortho-toluidine (risk of [O] Hb to Met-Hb) → Hydroxylated to 4- and 6-HO-toluidine - Negligible (< 1% excreted unchanged in urine) - Nb. Clearance ↓ with liver disease or ↓ HBF (Eg. CCF, β-blockers, GA)
Pharmacodynamics	
Dosing and effects	- Potency: + - Max. dose: 6 mg/kg (8 mg/kg with Felypressin); 400 mg as single bolus - Toxic plasma [LA]: > 5 µg/mL - Slow onset with intermediate duration (1-2 hrs)
Intrinsic vasodilator activity at low []	Prilocaine > lignocaine > bupivacaine > mepivacaine > ropivacaine * Nb. At high [] → Vasoconstrictor effect
Clinical uses	Regional anaesthesia (PND for dental procedures; IVRA)
Issues	(1) Dose-related methaemoglobinaemia limits its clinical use → O-toluidine metabolite accumulates when doses > 10 mg/kg used (2) ↑ systemic toxicity with liver disease or ↓ HBF (Eg. CCF, GA) (3) Allergies rare (often due to preservatives)

EMLA (Eutectic Mixture of LA):

Preparation	- 5% oil-in-water emulsion of 2.5% lignocaine and 2.5% prilocaine → Forms “eutectic mixture” whereby the melting point of the combined drugs is lower than each LA alone (I.e. mixture exists as an oil at room temperature, rather than a crystalline base of each constituent alone) - Contains Na ₂ CO ₃ buffer (base) → ↑ unionised fraction → ↑ absorption Eutectic mixture – Defined as mixing of two compounds to produce a substance that behaves with a single set of physical characteristics
Clinical uses	- Topical anaesthesia to allow vascular access (Eg. IVC, arterial lines), cautery of skin lesions, skin-graft harvest, circumcision, myringotomy, laser removal of portwine stains, Etc. - It acts by diffusing through intact keratinised skin (which is a significant

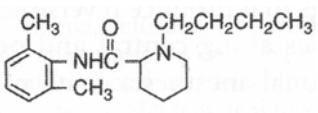
	barrier to drugs) → Inhibit neural conduction of dermal sensory receptors
Dosing and effects	- 1-2 g applied per 10 cm² of skin and covered with occlusive dressing for ~ 1 hour (although duration of application will vary on type of procedure and site of application; I.e. 2 hrs for skin-graft harvest vs 10 mins for cautery of warts) - Onset within 45 mins (although effect can be seen after 5 mins), with 1-2 hrs duration of action, and effect as deep as 3-5 mm - Factors affecting onset, duration and depth of penetration of EMLA: - (i) Skin blood flow - (ii) Skin thickness - (iii) Presence of skin pathology - (iv) Duration of application - (v) Total dose applied
Issues	- Localised vasoconstriction by constituents → Although it ↓ systemic absorption, it makes vascular access more difficult - EMLA should be avoided in certain situations: - (1) Patients at risk of methaemoglobinaemia (due to O-toluidine metabolite from prilocaine) – Known congenital/idiopathic methaemoglobinaemia, children < 3/12 old (due to immature RBC met-Hb reductase pathway), and concurrent use of met-Hb-causing drugs (Eg. GTN, SNP, sulphonamides, phenytoin) - (2) Use on mucous membrane or broken skin (due to faster LA absorption) - (3) Use on skin wounds (due to risk of infection) - (4) Concurrent use of class 1 antiarrhythmic drugs (Eg. mexiletine) - (5) Known allergy to amide LA (rare) - Local skin reactions (rash, blanching, pallor, erythema, oedema, pruritus) are rare

Bupivacaine:

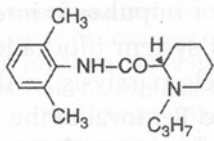
Type and structure	Amide LA – Pipecoxylylidide derivative (butyl group on piperidine N-group (amine)); exists as a racemic mixture Mwt. 288.4 g/mol 
Preparation	Bupivacaine HCl as clear colourless solution (0.25%, 0.5%) +/- adrenaline (1:200k); hyperbaric (“heavy”) preparation (0.5% bupivacaine HCl + 80 mg/mL glucose → SG 1.026) for spinal anaesthesia
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient 28 95% protein-bound (esp to A1AGP) pKa 8.1 (17% unionised at phgyl pH) Vd 0.7-1.3 L/kg
Metabolism and excretion	- Clearance 0.47 L/min/kg; t_{1/2} β 200 mins - Cleared mainly by hepatic metabolism – N-dealkylation to pipecolic acid and pipecolylxylidine (and also aromatic hydroxylation, amide hydrolysis, conjugation) - Minimal renal elimination (16% excreted unchanged in urine) - Nb. Clearance ↓ with liver disease or ↓ HBF (Eg. CCF, β-blockers, GA)

Pharmacodynamics	
Dosing and effects	- Potency: +++++ - Max. dose: 2-2.5 mg/kg (+/- Adr); 150 mg as single bolus or 400 mg per 24 hrs - Toxic plasma [LA]: > 3 µg/mL - Slow onset (15-20 mins) with long duration (4-8 hrs)
Intrinsic vasodilator activity at low []	Prilocaine > lignocaine > bupivacaine > mepivacaine > ropivacaine * Nb. At high [] → Vasoconstrictor effect
Clinical uses	Regional anaesthesia (infiltration, PNB, SAB, EDB) - More differential sensory blockade with sparing of motor blockade - Longer duration of action (cf. other LAs) → Adr does not alter rate of absorption as drug is highly lipid soluble (I.e. rapid uptake) and drug has innate vasodilatory effect - ↑ systemic toxicity (esp cardiac) → Cannot be used for IVRA - ↓ crosses placenta due to ↑ protein binding (except during foetal acidosis due to ↑ ion trapping)
Issues	(1) Most cardiotoxic LA → Resistant to resuscitation (2) Most myotoxic (causes myonecrosis) when injected directly (3) ↑ systemic toxicity with liver disease or ↓ HbF (Eg. CCF, GA) (4) Allergies rare (often due to preservatives)

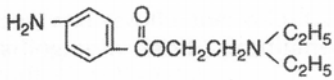
Levobupivacaine:

Type and structure	Amide LA – Pipecoxyliide derivative (butyl group on piperidine N-group (amine)); exists as pure S-isomer Mwt. 288.4 g/mol 
Preparation	Levobupivacaine HCl as clear colourless solution (0.25%, 0.5%, 0.75%) → No adrenaline
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient ? (but less than bupivacaine!) > 97% protein-bound (esp to A1AGP) pKa 8.1 (17% unionised at phgl pH) Vd 0.7-1.3 L/kg
Metabolism and excretion	Similar to bupivacaine
Pharmacodynamics	
Dosing and effects and intrinsic vasodilator activity	Similar to bupivacaine
Clinical uses and issues	Similar to bupivacaine EXCEPT: - ↓ systemic toxicity (30-50% less CNS and CVS toxicity) due to ↓ lipid solubility - Even less motor blockade due to ↓ lipid solubility, but at expense of slower onset, shorter duration of effect and less dense sensory blockade

Ropivacaine:

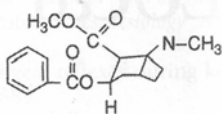
Type and structure	Amide LA – Pipecoxylicide derivative (propyl group on piperidine N-group (amine)); exists as pure S-isomer Mwt. 328.8 g/mol 
Preparation	Ropivacaine HCl as clear colourless solution (0.2%, 0.5%, 0.75%, 1%) → No adrenaline
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient 2.9 94% protein-bound (esp to A1AGP) pKa 8.1 (17% unionised at physiological pH) Vd 0.7-1 L/kg
Metabolism and excretion	- Clearance 0.8 L/min; $t_{1/2}$ 60-170 mins - Cleared mainly by hepatic metabolism – Aromatic hydroxylation to 2,6-pipecoxylidide and 3-HO-ropivacaine (active metabolite with ↓ potency than parent drug) → Former can accumulate in renal failure and cause toxicity - Negligible renal elimination (< 1% excreted unchanged in urine) - Nb. Clearance ↓ with liver disease or ↓ HBF (Eg. CCF, β-blockers, GA)
Pharmacodynamics	
Dosing and effects	- Potency: ++++ - Max. dose: 2-3 mg/kg; 200 mg as single bolus - Toxic plasma [LA]: > 4 µg/mL - Slow onset (15-20 mins) with long duration (4-8 hrs)
Intrinsic vasodilator activity at low []	Prilocaine > lignocaine > bupivacaine > mepivacaine > ropivacaine * Nb. At high [] → Vasoconstrictor effect
Clinical uses	(1) Use in regional anaesthesia similar to bupivacaine EXCEPT: - NOT intended for use in SAB - ↓ systemic toxicity due to ↓ lipid solubility - Less motor blockade due to ↓ lipid solubility, but at expense of slower onset, shorter duration of effect and less dense sensory blockade (2) ↓ bronchial reactivity and prevent bronchospasms
Issues	(1) Still relatively cardiotoxic → Cannot be used for IVRA (2) Vasoconstrictor property (esp at high doses) → Prolongs cutaneous analgesia (BUT negligible effect for PNB) but carries risk of end-organ ischaemia (3) Toxicity 2° to 2,6-pipecoxylidide metabolite with renal dysfunction (4) ↑ systemic toxicity with liver disease or ↓ HBF (Eg. CCF, GA) (5) Allergies rare (often due to preservatives)

Procaine:

Type and structure	Ester LA. Mwt. 236 g/mol 
Preparation	Procaine HCl as clear colourless solution (1%, 2%, 10%)
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient 0.6

	6% protein-bound pKa 8.9 (3% unionised at phgyl pH) Vd 0.7 L/kg
Metabolism and excretion	- Clearance ?; $t_{1/2} \beta$ 9 mins - Cleared by hepatic metabolism – Hydrolysed to para-aminobenzoic acid (excreted in urine unchanged) and diethylaminoethanol (further metabolised) - < 50% excreted unchanged in urine
Pharmacodynamics	
Dosing and effects	- Potency: + - Max. dose: 10 mg/kg; 500 mg as single bolus - Toxic plasma [LA]: > 5 µg/mL - Slow onset with intermediate duration (0.5-1 hrs)
Clinical uses	(1) Use in regional anaesthesia (infiltration, PNB, SAB) (2) Adjunct to GA (used for analgesia and MAC-sparing effects)
Issues	(1) ↑ allergic risk (due to PABA metabolite) (2) Relatively short duration of action (3) Myotoxicity when injected directly into muscle (4) ↑ systemic toxicity with deficiency in plasma and liver cholinesterase deficiency

Cocaine:

Type and structure	Ester LA – Derived from Erythroxylon coca. Mwt. 303 g/mol 
Preparation	Clear colourless solution (1-4%); pastes of varying concentrations
Pharmacokinetics	
Distribution	Lipid solubility: Hexanol:buffer coefficient ? (similar to lignocaine) 98% protein-bound pKa 8.7 (5% unionised at phgyl pH) Vd 0.9-3.3 L/kg
Metabolism and excretion	- Clearance 25-40 mL/min/kg; $t_{1/2} \beta$ 60-90 mins - Metabolised by plasma esterases, but also undergoes extensive hepatic metabolism by hydrolysis (via esterases) and N-methylation into water-soluble metabolites (excreted in urine) - Minimal renal elimination (10% excreted unchanged)
Pharmacodynamics	
Mechanism of action	(1) Inhibition of VG- Na^+ channels (See MOA for LAs above) (2) Enhances DA and NAd nerve terminals (centrally and peripherally) → Inhibits presynaptic uptake of NAd/DA (antagonises uptake-1) and inhibits MAO → Maintains synaptic levels of NAd/DA
Dosing and effects	- Potency: ++ - Max. dose: 3 mg/kg - Toxic plasma [LA]: > 0.5 µg/mL - Intermediate onset (30 mins) with short duration (0.5-1 hrs)
Intrinsic vasodilator activity at low []	Cocaine has intrinsic vasoconstrictor effect at ALL []
Clinical uses	Mainly used for topical anaesthesia as it is well absorbed from mucous membranes and possesses localised vasoconstrictor activity → Ideal for ENT cases and airway manipulation (Eg. FOB/DL intubations)

Adverse effects	(1) CVS effects → Due to ↑ central SNS stimulation and ↑ peripheral NAd activity which causes: - Coronary vasospasms - Myocardial ischaemia (due to ↓ blood supply 2° coronary vasospasms, and ↑ O₂ demand 2° ↑ HR and BP) - HTN and tachycardia - Ventricular arrhythmias (including VT/VF) - CVA (haemorrhagic or ischaemic) Note: • These effects can be exaggerated if cocaine + adrenaline is used (esp in presence of VAs such as halothane → sensitises myocardium) • Avoid cocaine if underlying CVS disease (arrhythmias, IHD, HTN) or drugs that can potentiate catecholamines (MAOis, VAs) (2) CNS effects – Euphoria; Biphasic effect similar to LAs (stimulatory effects, followed by depressive effects) (3) Respiratory effect – Initially ↑ ventilation 2° to medullary stimulation, then later respiratory depression/apnoea 2° to medullary depression (4) GIT effects – Marked N/V, risk of GIT infarction (2° vasoconstriction) (5) Hyperpyrexia (2° to central hypothalamic effect and ↑ motor activity) (6) ↑ IOP (7) Drug dependence/addiction (8) Risk of foetal hypoxaemia 2° to dose-dependent ↓ in uterine BF
Treatment of cocaine toxicity	- GTN for myocardial ischaemia - SNP to treat HTN - α-antagonist for coronary vasospasms - β-blockers to treat HTN/tachycardia (but risk of worsening coronary vasospasms and causing profound CVS collapse/arrest)