# REGIONAL AND LOCAL ANAESTHESIA

# Describe the physiology of nerve conduction

## *Resting membrane potential*

**Outline the factors contributing to the generation and maintenance of the resting membrane potential: PAST QUESTION**

**Neural tissue** (Neurons):
- 2 characteristic structural + functional features: excitable membrane, + synapses
- Excitability = ability of neurons to generate + propagate electrical impulses (AP)
- Synapses = specialised points of communication that allow neurons to communicate with each other

**RMP**
- The membrane potential of the cell = the electrical voltage of interior relative to exterior
- RMP = -70mV in nerve; -90mV in skeletal muscle cells

***How is the membrane potential produced?***

RMP is generated by uneven distribution of charged particles (i.e. ions and proteins) across the cell membrane 2o to:

1. **Semi permeable membrane / selective membrane permeability to different ions**
   - At rest CM is:
     - Slightly permeable to Na: Na channels closed
     - Very permeable to K: open K+ leak channels → K down conc gradient from ICP to ECF
     - Variable permeability to Cl based on cell type
2. **Different ionic concentrations of ICF and ECF**
   - Na+: 140mmol/L ECF; 20mmol/L ICF
   - K+: 150mmol/L ICF; 5mmol/L ECF
   - Na/K ATPase: 3Na+ out for 2K+ in. Consequences:
     - Osmotic effect: ↑ECF [Na+] balances osmotic effect of ↑intracellular conc of –vely charged protein
     - Electrogenic effect: cell interior hyperpolarised
3. **Gibbs Donnan effect**
   - Minor contribution to RMP
   - unequal distribution of large –vely charged protein impermeable to CM → affects distribution of other diffusible ions (K, Cl) and hence RMP by ~-10mV

***Principles***

1. **Nernst equation**
   - Nerst potential: voltage difference generated by EC gradient of an ion across CM (assuming complete permeability) i.e. contribution that a single ion makes to RMP
   - Calculated from valency, conc difference across membrane, and temp
   - The ion with ↑membrane permeability → Nerst potential has ↑contribution to total RMP
   - Nernst applied:
     - RMP has ↑K permeability → net efflux of +vely charged K down conc gradient → drives membrane potential towards Nernst potential for K+
     - RMP ↓permeability to Na+ ions
     - Therefore: measured neuronal RMP (-70mM) = close to Nernst potential for K+
2. **Goldman –Hodgkin-Katz equation**
   - considers all ionic permebailities and concentrations → RMP more precisely quantified
3. **Gibbs Donnan effect**

**Key equation: the Goldman–Hodgkin–Katz equation**

$$E_m = \frac{RT}{F} \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

where $E_m$ (mV) is the calculated membrane potential and $P_X$ is the permeability of the membrane to ion X.

Note:
- If the membrane is permeable only to $K^+$, then $P_{Na}$ and $P_{Cl}$ equal zero and the equation reduces to the Nernst equation for $K^+$.
- There is no valency term as only monovalent ions are considered.
- The concentrations of $Cl^-$ are shown opposite to those of $K^+$ and $Na^+$ to account for its negative valency.

***Typical RMPs of various cells***

| Cell type | RMP (mV) |
|---|---|
| Myelinated Axon | –70 |
| Skeletal muscle | –90 |
| Cardiac myocyte | –80 |
| Cardiac pacemaker | nil fixed RMP (prepotential –60) |
| Smooth muscle | nil fixed RMP (–20 to –60) |

**Key equation: the Nernst equation**

$$E_X = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

where $E_X$ (mV) is the Nernst potential for a particular ion, $R$ is the universal gas constant (8.314 J/(K mol)), $T$ (K) is the absolute temperature, $F$ is the Faraday constant, the electrical charge per mole of electrons (96 500 C/mol), $z$ is the valency of the ion, $[X]_o$ (mmol/L) is the ion concentration outside the cell and $[X]_i$ (mmol/L) is the ion concentration inside the cell.

## *Action potential*

**General**
- AP = electrical response of neurons and other excitable tissues during which membrane potential rapidly ↑ and ↓
- All or nothing phenomenon
- Allow rapid signalling within excitable cells over long distances
- AP results from brief ↑ in membrane conductance to Na+, followed by slower ↑in membrane conductance to K+
- Key parameters
  - RMP -70mV
  - Threshold potential -55mV
  - Peak potential (depolarisation) +20-40mV
  - Duration of AP 1-2ms

**Physiological basis**

***RMP***
- uneven distribution of charged particles (i.e. ions and proteins) across the cell membrane 2o to:
- maintained by:
  - Selective permeability of membrane to different ions
  - Different ionic concentrations of ICF and ECF
  - Gibbs donnan
- Principles
  - Nernst
  - Goldman Hodgkin Katz
  - Gibbs donnan

***Events of an AP***:
- **Phase 1 - threshold potential**: depolarisation stimulus reaches neuron → CM reaches -55mV → activation of voltage gated Na+ channels → Na+ influx > K+ efflux

- **Phase 2 – AP**: rapid influx of Na → further depolarisation → +ve feedback → rapid upstroke → drives membrane potential to Nernst potential for Na of ~+50mV → peak potential +30mV
- **Phase 3 - repolarisation**: AP never reaches theoretical max (+50mV) due to 2 events:
  - 1. Inactivation of voltage gated $Na^+$ channels → ↓membrane permeability to $Na^+$
  - 2. Delayed activation of voltage gated $K^+$ channels: ↑membrane $K^+$ permeability → $K^+$ efflux → membrane potential driven back towards Nernst for $K^+$ of ~-90mV
  - Membrane potential briefly more –ve than RMP = "after hyperpolarisation" - due to gradual closure of voltage-gated $K^+$ channels
- **Phase 4 – restoration of RMP**
  - -70mV maintained by: Na/K ATPase (EC gradient) + Na/K pump

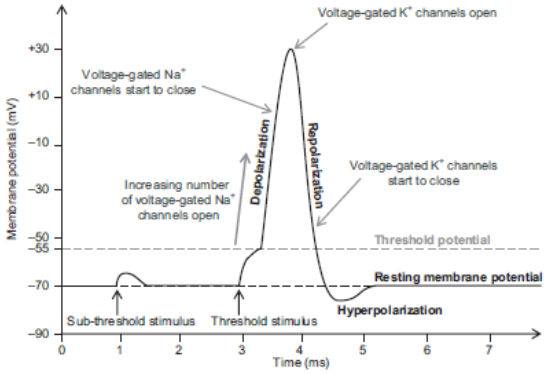



**Figure 49.1** The nerve action potential.

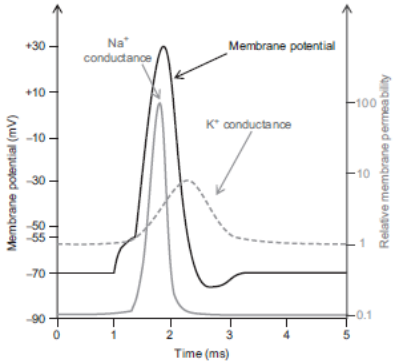
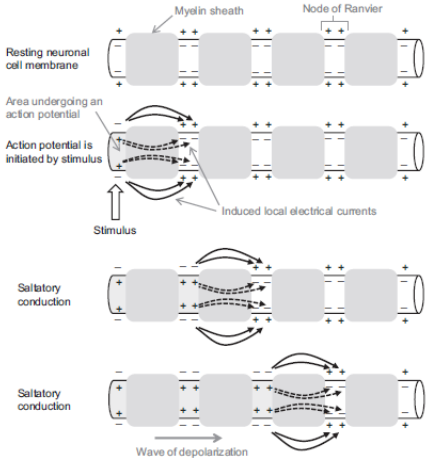



**Figure 49.2** Changes in the membrane permeability of $Na^+$ and $K^+$ throughout the action potential.

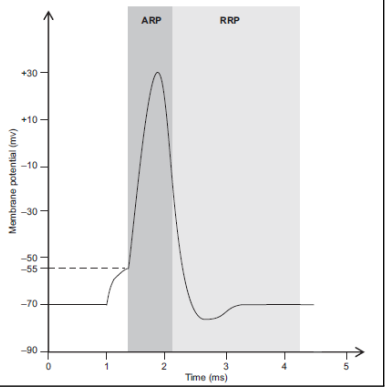
***Conduction of nerve impulses: Saltatory conduction***

- Electrical depolarisaiton propagates by formation of local circuits
  - Intracellular surface of resting portion of CM–vely charged
  - following AP → the portion of CM depolarises → intracellular surface +vely charged
  - ion movement at edges of the depolarised CM → current flow → neighbouring portions of C
- Velocity of conduction is dependent on several factors:
  - Axon diameter: ↑diameter → ↓resistance to flow → ↑conduction velocity
  - Transmembrane resistance:↑resistance → ↓loss of current flow → ↑conduction
  - Membrane capacitance: ↑capacitance → longer to alter polarity → ↓speed of propagation.
  - Temperature: ↑temp → ↑rate Na+ channel opening → ↑velocity
- Myelin
  - Produced by Schwann cells (PNS) + oligodendrocytes (CNS)
  - Nodes of Ranvier = exposed regions of membrane densely populated with voltage gated Na
  - Electrical impulse propagates across internode by local circuit conduction
  - Role:
    - Important determinant of nerve conduction velocity
    - Insulates axon: ↑transmembrane resistance; ↓loss of current to ECF
    - ↓effect of membrane capacitance
    - Saltatory conduction




***Refractory period***

- Time following an AP
- 1. ARP:
  - AP cannot be triggered whatever the size of the stimulus
  - starts from when voltage-gated Na+ channels open → continues until repolarisation 1/3 complete
- 2. RRP:
  - Repolarisation: K leak channels + voltage gated K channels open = K permeability is highest
  - AP only with ↑↑stimulus to counteract ↑K+ efflux
- Important for 2 reasons:
  - 1. Ensure unidirectional propagation of Aps
  - 2. Limiting frequency of APs




## *Synaptic function*

Synapse = functional point of contact between 2 excitable cells, across which a signal can be transmitted.

***2 types of synapse:***

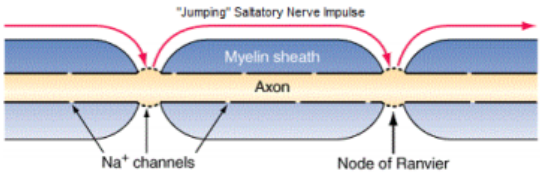
- **1. Chemical synapse**
  - Signal relayed by chemical messenger (neurotransmitter)
  - Arrival of AP triggers NT release inot synaptic cleft → excites or inhibits post-synaptic cell
  - Unidirectional
  - Eg NMJ
- **2. Electrical synapse**
  - Pre + post synaptic cells are joined by gap junctions that allow electrical current to pass
  - AP in pre-synaptic cell induces local current in post-synaptic cell → triggers AP
  - Bidirectional
  - Eg cardiac muscle

## *What is salutatory conduction and what are the advantages of this type of conduction: PAST QUESTION*

***General***

- Saltatory conduction: propagation of AP along myelinated axons, whereby wave of depolarisation "jumps" from one rode of Ranvier to the next

- Myelin
  - lipoprotein produced by oligodendrocytes (CNS) + Schwann cells (PNS)
  - myelin sheaths wrap around axons → interrupted at regular intervals (1-3mm) → exposing nodes of Ranvier
- Nodes of ranvier
  - Contain dense population of fast Na+ channels




***Mechanism of saltatory conduction***

- Depolarisation of a node → influx of Na ions → creating a sink (area of –ve charge at the surface)
- +ve charge on nodes ahead flows into sink → ↓polarity inside the membrane → AP → propagating current activates fast Na channels → wave of depolarisation down axon
- minimal electrical signal degradation as axon is insulated by myelin sheath
- AP reaches next node of Ranvier → continues down myelinated fibre
- Nerve impulses appear to rapidly jump from one node to the next

***Advantages***

- Faster
  - myelinated axons can propagate impulses over long distances at faster rate, without degradation of signal
  - conduction velocity of unmyelinated fibres = 2m/s vs. myelinated 200m/s
  - for a given fibre diameter → myelinated conduction velocity >> unmyelinated
- More energy efficient
  - Depolarisation largely localised to nodes of Ranvier → less ion flux required for conduction → ↓energy consumption by Na/K/ATPase to restore ion gradients → ↓energy required

## *Write notes on the axonal membrane: PAST QUESTION*

***Axon***

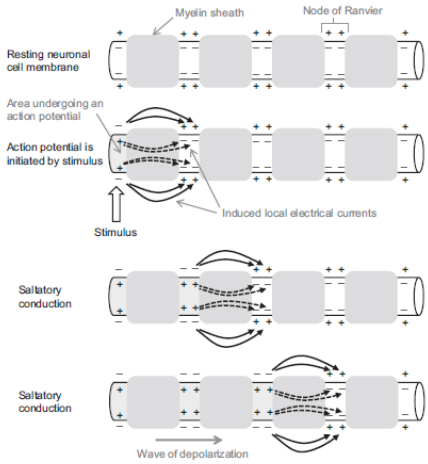
- fibre like structure that leaves the cell body
- contains mitochrondria, microtubules, and SR
- terminals contain small vesicles packed with NT

***Axonal membrane***

- cell membrane which envelops the cytoplasm of an axon, separating cellular contents from ECF; bathed in ICF

***Activation: saltatory conduction***

- Electrical depolarisaiton propagates by formation of local circuits
- AP at one point in nerve axon sets up local electrical currents in adjacent resting membrane
  - Intracellular surface of resting portion of cell membrane–vely charged
  - AP → portion of CM depolarises → intracellular surface +vely charged
  - ion movement at edges of depolarised CM → current flow → depolarise adjacent membrane towards threshold → new AP fired
  - process continuous down axon + AP popagates form one end of nerve to other
- Velocity of conduction dependent on several factors:
  - Axon diameter: ↑diameter → ↓resistance to flow → ↑conduction velocity
  - Transmembrane resistance:↑resistance → ↓loss of current flow → ↑conduction
  - Membrane capacitance: ↑capacitance → longer to alter polarity → ↓speed of propagation.
  - Temperature: ↑temp → ↑rate Na+ channel opening → ↑velocity




***Types of axons***

- 2 types of axons: unmyelinated and myelinated
- Myelin
  - Produced by Schwann cells (PNS) + oligodendrocytes (CNS)
  - Nodes of Ranvier = exposed regions of membrane densely populated with voltage gated Na channels
  - Electrical impulse propagates across internode by local circuit conduction
  - Role:
    - Important determinant of nerve conduction velocity
    - Insulates axon: ↑transmembrane resistance; ↓loss of current to ECF
    - ↓effect of membrane capacitance
    - Saltatory conduction

## *Explain the physiological mechanisms whereby an action potential arriving at a synapse might not be conducted: PAST QUESTION*

***Background***

- AP = electrical response of neurons and other excitable tissues during which its membrane potential rapidly ↑and ↓
- Synapse
  - junction between a neuron and another cell (e.g. nerve, muscle) where a chemical (or electrical) signal is communicated
  - Consists of:
    - Presynaptic terminal: vesicles containing NTs → released by exocytosis in response to AP
    - Synaptic cleft: junction where NTs are released
    - Post synaptic membrane: contains receptors to which NT may bind → post synaptic stimulation

***Reasons for non-conduction of AP***

1. **Post synaptic refractoriness**
   - After post-synaptic membrane depolarisation → need repolarisation before being able to undergo another depolarisation
   - 2 types:
     - ARP: post synaptic membrane unable to reach threshold irrespective of stimuli

        - RRP: need supramaximal stimuli to reach threshold
2. **Summation of EPSP not reaching threshold**
    - EPSP: partial depol in postsynaptic neuron → ↑excitability
    - Post synaptic membrane only depolarises when sum of EPSPs > threshold
    - Summation:
        - Spatial: activity from >1 synaptic knob facilitating another
        - Temporal: repeated stimuli producing new EPSP before previous EPSP decayed
    - If AP unable to generate combined EPSP > threshold → will not be propagated → failure of synaptic transmission
3. **Inhibitory post-synaptic potentials**
    - Inhibitory interneurons → ↑Cl channels → IPSP → post synaptic membrane hyperpolarisation → need greater summation of EPSP to reach threshold
4. **Presynaptic inhibition**
    - Axo-axonal synapses; GABA released → opens Cl channels, ↓amplitude of AP, or ↓excitatory transmitter release
5. **Presynaptic NT exhaustion**
    - Rapid repeated stimulation → deplete presynaptic NT + vesicles > rate of synthesis → synaptic fatigue → further APs unable to release NTs

***NB summary of electrochemical events during synaptic transmission***
(1) AP propagates down axon to presynaptic terminal
(2) Exocytosis of NTs
(3) NT diffuses across synaptic cleft + bind receptors on post-synaptic membrane
(4) Small depolarisation of post-synaptic membrane → excitatory post-synapticpotential (EPSP) → not enough to reach threshold
(5) Multiple EPSPs temporally + spatially summate to achieve threshold potential in post-synaptic membrane → propagation of signal

## *Explain how lignocaine prevents the conduction of a nerve action potential: PAST QUESTION*

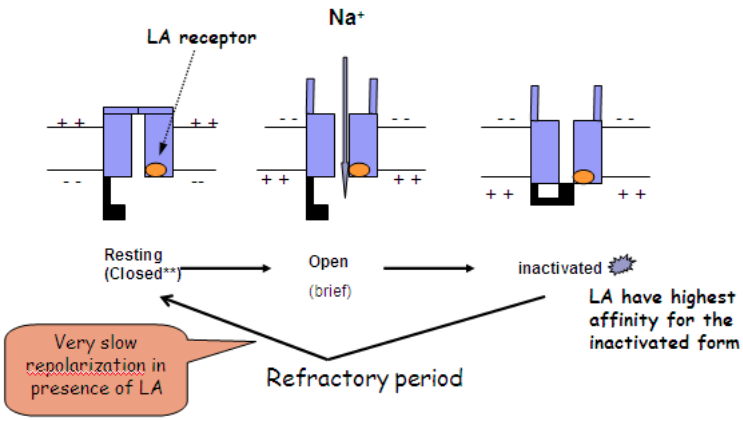
***Background***
- lignocaine = weak amide LA with pKa 7.9
- used in local infiltration/ regional / neuraxial anaesthesia
- primary MoA = blockage of voltage gated Na+ channels

***How lignocaine reaches target nerve***
- local infiltration or topical application → unionised + non-PB fraction diffuse to reach target nerve
- diffusion follows **ficks law of diffusion**

$$\text{Rate of diffusion} = \frac{area}{thickness} \times \frac{sol}{\sqrt{MW}} \times conc\ gradient$$

- Factors that affect onset of action include:
    - Drug factors
        - Concentration + volume added
        - MW
        - pKa + effect on non-ionised fraction:
            - only unionised fraction is soluble and able to cross lipid bilayer.
            - ↓pKa → ↑unionised fraction
        - lipid solubility + effect on potency + PB
    - Patient factors
        - Site of administration + diffusion distance/ diffusion area
        - Nerve structure + function
        - Protein binding
        - Tissue pH + electrolyte disturbances

***Mechanism of action***
- Lignocaine deposited near target nerve
- Free (unionised, non-PB) lignocaine molecules diffuse across axonal membrane (phospholipid bilayer)
- Lignocaine in axoplasm binds specific LA binding site on internal surface of voltage gated Na+ channels
- **Binds Na+ in inactivated-closed state** → inhibit further conformational change → prevents Na+ channel activation → blockade of nerve impulse transmission
- Initial impulse block (tonic block) = incomplete → partially blocked fibres are further inhibited with repetitive stimulation (phasic block)
- After lignocaine enters axoplasm, it becomes protonated + ionised → ionised LA exhibits **frequency dependent blockade** i.e. it will only bind to Na channels at a rate proportional to rate of stimulation




**Closed state may exist in various forms as it moves from resting to open. LA have a high affinity for the different closed forms and may prevent them from opening.

***Nature of blockade / differential nerve block***
- Cm = minimal conc of lignocaine required to achieve blockade

- Dependent factors:
  - Fibre size: smaller, shorter nerves blocked before larger
  - Fibre type: differential blockade: B (autonomic) > Adelta (nociceptive) > Aα (motor) >C (visceral/pain/ slowest)
  - Myelination: myelinated fibres (saltatory conduction) → blocked before non-myelinated fibres
  - more frequent firing fibres are blocked before less frequent fibres
  - Fibre location: spinal anaesthetic ↓Cm cf epidural
  - tissue pH: ↓pH → ↑Cm

## Discuss the pharmacology of local anaesthetic agents including: • Mechanisms of action • Comparative pharmacology of different agents • Toxicity • Use of adjuvant agents to enhance the quality or extend duration of block • Pharmacokinetics of drugs administered in the epidural and subarachnoid space

### *MoA local anaesthetics*

- LA create a use-dependent termporary blockade of neuronal transmission by blocking the volatage-gated Na+ channel in the cell membrane → preventing depolarisation
- All local anaesthetics are weak bases consisting of:
  - Hydrophilic component
  - Lipophilic aromatic ring
  - Amide or ester link connecting the 2

**MOA**

- **Na+ channels**
  - Prevention of Na+ conduction:
    - LA diffuses from site of injection to axon
    - LA crosses axon membrane in **unionised form** → converted to **ionised form** in axoplasm 2o ↓pH
    - Ionised form binds to internal surface (H gate) of Na+ channels → Na+ channels remain in inactive state → slows rate of depolarisation + prolongs absolute refractory period → threshold potential not reached → AP not propagated
  - Mechanical distortion of channel → channel ineffective
- Other sites of action:
  - **Voltage gated K+ channels:** lower affinity
  - **Voltage gated Ca2+ channels:** L type ↑sensitive
  - May also act on GPCRs

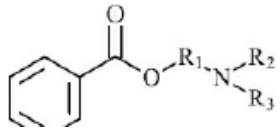
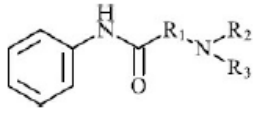
***Frequency dependent blockade***

- LA have ↑access to Na+ channels when in activated (open) state → ↑nerve firing means easier access of LA to binding site of Na+ channels
- May play role in differential blockade: selective conduction blockade of different types of nerve fibres
- Onset of nerve block:
  - B > C + Adelta > Aγ > Aβ > Aα
  - I.e: pain > cold + warmth > touch > deep pressure > motor function

### *Classification of local anaesthetics based on chemical structure of intermediate linkage chain*

| Esters | Amides |
|---|---|
| Ester linkage (R-CO-O-R1)<br>E.g. procaine, amethocaine, cocaine | Amide linkage (R-NH-CO-R1)<br>E.g. lignocaine, bupivacaine, ropivacaine, dibucaine, prilocaine |

### *Structure activity relationships of LAs*

- **Hydrophilic portion** (usually tertiary amine): determines degree of ionisation
- **Lipophilic portion** (usually aromatic ring): ↑lipid solublity → ↑potency, DoA, toxicity
- **Intermediate hydrocarbon chain**
  - Ester linkage
    - 
    - R-CO-O-R1
    - Unstable in solution
    - Rapidly hydrolysed by plasma cholinesterase to para-amino-benzoic acid (PABA)
    - PABA associated with hypersensitivity reactions
  - Amide linkage
    - 
    - R-NH-CO-R1
    - Stable in solution
    - Slower hepatic metabolism
    - Hypersensitivity reactions rare
  - ↑length → ↑lipid solubility
- **Isomerism**
  - Bupivacaine: racemix mix of S and R enantiomer
  - Levobupivacaine: S-enantiomer of bupivacaine; ↓toxic
  - Ropivacaine: pure S-enantiomer; R-enantiomer ↓potent + ↑toxic

### *Pharmaceutics of local anaesthetics: MAKEUP*

Bupivacaine

- Formulated as hydrochloric acid salts to ↑water solubility
- Contain preservatives e.g. Na bisulphite (strongy acidic)
- Additives:
    - Adrenaline: catecholamines unstable in alkaline environment
    - Opioids
    -
-

## *Factors affecting the speed of onset and duration of effect of local anaesthetics when used to produce peripheral nerve block: PAST QUESTION*

***Background***

- LA = drug that inhibit transmission ofnerve impulses in applied region without affecting level of consciousness
- MoA:
    - LAs diffuse across phospholipid bilayer of the nerve fibre → enter axoplasm
    - Protonated + ionised → binds internal surface of voltage gated Na channels (while in activated open state)
    - Maintains the inactivated closed state → inhibit nerve impulse propagation
- Other minor MoA:
    - LAs bind to external opening of Na channel to facilitate above mechanism
    - LAs dissolve in phospholipid bilayer → expansion → disrupt Na channel structure

**Factors affecting SPEED OF ONSET**

- Depends on rate of diffusion of LA from site of injection to within target nerve fibre
- Governed by **Fick's law of diffusion:**
    - $\text{Rate of diffusion} = \frac{area}{thickness} \times \frac{sol}{\sqrt{MW}} \times conc\ gradient$
- **Drug factors**
    - pKa (1o factor)
        - Ionised drugs = poorly lipid soluble → ↓onset of action
        - LAs = weak base: ↓pKa = ↑absorption into nerve tissues; ↑pKa = ↑effective within nerves
        - ↓pKa → ↑unionised fraction
    - MW: ↓MW → ↑diffusion → faster onset (NB all have similar MW therefore little impact on diffusion)
    - Lipid solubility and effect on potency + PB: ↑lipid solubility → ↑diffusion → faster onset
    - Concentration gradient + vol added
        - ↑dose → ↑conc gradient → ↑diffusion → faster onset
        - ↑vol → ↑area of contact with target nerve → ↑diffusion → faster onset
    - Diffusion distance
    - Area of diffusion
    - Alkalinisation: adding NaHCO3 → ↑unionised fraction → ↑onset of action
- **Patient factors**
    - Site of administration
        - ↓diffusion distance → ↑diffusion → faster onset. Depends on location of injection + proximity to target nerve
    - Nerve structure + function
        - ↑nerve diameter → ↑diffusion distance → slower onset
        - ↑nerve firing rate → ↑onset of action (frequency dependent blockade_
        - myelinated fibres blocked faster than unmyelinated fibres (continuous conduction)
        - order of onset: β > Adelta >Aβ > Aα > C (slowest); autonomic >pain/sensory > motor
    - ↓α1-acid glycoprotein → unbound LA → faster onset
    - Tissue pH + electrolyte disturbances
        - acidosis → ↑ionised fraction → ↓lipid solubility → slower onset (i.e. infected tissue → slower onset)
        - hyperkalaemia → membrane depolarisation → more Na+ channels in active state → potentiates LAs → faster onset
    - Pregnancy

**Factors that affect DURATION OF ACTION**

- **Drug factors**
    - Protein binding (1o factor)
        - ↑PB → longer binding to neuronal membrane proteins → ↑DoA
        - e.g. lignocaine 70% vs. bupivacaine 95%
    - Intrinsic vasodilator activity
        - ↑vasodilation → ↑systemic absorption → ↓DoA
        - vasodilators: prilocaine > lignocaine > bupivacaine > ropivacaine
        - vasoconstrictors: cocaine
    - Lipid solubility
        - ↑lipid solubility → ↑potency; ↑sequestration into lipid rich compartments (↓drug availabile for metabolism); ↑PB → ↓free fraction
    - Additives
        - Adrenaline: vasoconstriction
        - Clonidine: ↑DoA spinal, epidural, peripheral nerve blocks
        - Opioids: ↑DoA spinal + epidural
    - Dose
    - ↑pKa → ↑ionised fraction → ↑ion trapping within axoplasma → ↑duration
- **Patient factors**
    - Site of administration:
        - ↑regional blood flow → ↑systemic absorption, ↓DoA
        - Systemic absorption in order of ↓ rate: intercostal > caudal > epidural > peripheral nerve > subcut infiltration
    - Metabolism
        - faster metabolism → ↓duration of action. In general esters have shorter DoA than amides
        - active metabolites → ↑duration of action e.g. ropivacaine → 3-hydroxyropivacaine (active)

## *Potency of local anaesthetics: MAKEUP*

***Minimum effective concentration of LA (Cm)***

- minimum concentration of a LA that results in complete block of a nerve fibre in 50% of subjects under standard conditions
- measure of potency: ↑potency → ↓Cm
- factors that affect Cm:
  - lipid solubility: ↑lipid solubility → ↓Cm
  - nerve fibre diameter: ↑diameter → ↑Cm
  - tissue pH: ↑pH → ↓Cm
  - frequency of nerve stimulation: ↑frequency → ↓Cm
  - pregnancy: ↑sensitivity may be present

**Factors affecting potency of LAs**

- **lipid solubility (1o factor)**
  - determines potency
  - potency = minimum amount of drug required to produce given effect
  - ↑lipid solubility → ↑molecules able to penetrate the nerves → less drug required to give same blockade
- **intrinsic vasodilatory activity**
  - all are vasodilators except cocaine, ropivavaine, and levobupicacaine = vasoconstrictors
  - degree of vasodilation influences toxicity + potency of LA
  - ↑vasodilation → ↑systemic absorption
- **Additives**
- **Tissue pH**
- **Tissue distribution**

***Pharmacodynamics***

- effects: reversible conduction blockade of nerve impulses along nerve pathways
- unionised form crosses to inside nerve membrane → ionised + binds to open active or inactive state of voltge gated Na channel, preventing Na flux + propagation of AP

**NB**

- **pKa**
  - pKa of a chemical compound represents the pH at which its ionised and non-ionised forms are in equilibrium
  - pKa of LA determines SOO as only uncharged form is lipid soluble and able to diffuse across myelin layers of nerve fibres
  - LA = weak bases but are injected in acidic solutions as hydrochloric salts
  - Tertiary amine (hydrophobic or water insoluble) becomes quaternary → soluble in water → suitable for injection
  - At physiological pH, proportion of drug that dissociates into free base (which is lipid soluble) is determined by its pKa → non-ionised portion passes through lipid cell membrane to inner axon where re-ionisation occurs → re-inoised portion of LA blocks Na channels
  - Closer the pKa of the drug is to physiological pH (7.4) → the ↑free base (non-ionised drug) present → faster block
  - than bupivacaine. Ropivacaine has ↓lipid solubility → ↓affinity + penetration of myelin sheath → blockade of C fibres > A fibres

## *Pharmacokinetics of local anaesthetics: MAKEUP*

***Factors that affect systemic absorption***

- physicochemical properties
  - pKa
  - lipid solubility: biphasic absorption; sequestration into lipid rich tissues
  - PB
  - Intrinsic vasodilator activity
- Vasoconstrictor
- Site of administration: different regional blood flow; intercostal > caudal > epidural > brachial plexus > spinal > SC
- Rate of ↑[plasma]

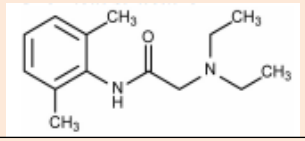
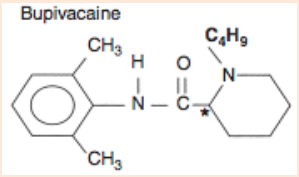
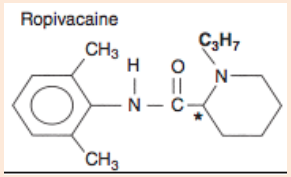
***Factors that affect distribution***

- PB
  - Parallels lipid solubility
  - Amides > esters
  - Bupivacaine > ropivacaine > lignocaine > prilocaine
  - α1-acid glycoprotein: ↑affinity
  - albumin: ↑capacity
- Regional blood flow
- Placental transfer: ↑PB → ↓transfer; ion trapping
- Lung extraction from circulation

***Metabolism + elimination***

- esters
  - Rapidly hydrolysed by plasma cholinesterases + other esterases → inactive metabolites; NB PABA → hypersensitivity reactions
  - ↓plasma cholinesterase activity → ↓metabolism + ↑risk systemic toxicity
  - cocaine: hepatic hydrolysis; inactive metbaolites; renal excretion
- Amides
  - Hepatic N-de-alkylation + hydroxylation
  - Slower metabolism → ↑accumulation → ↑risk toxicity
  - ↓hepatic blood flow/ dysfunction → ↓metabolism
  - minimal renal excretion of unchanged drug

*Amides*

| | Lignocaine | Bupivacaine | Ropivacaine | Prilocaine |
|---|---|---|---|---|
| Chem | Tertiary amine; lipophilic aromatic ring, amide linkage, hydrophilic tertiary amine<br>Achiral<br>pH 6.4<br>MW234<br>  | **Pipecoloxylide** → chiral centre<br>**Butyl** side chain → ↑↑lipid solubility + PPB<br>MW 288<br>  | **Pipecoloxylide** → chiral centre<br>**Propyl** side chain (cf bupivacaine - bupyl) → ↑lipid solubility<br>MW 274<br>  | Amide derivative of toluidine |
| MW | 234 | **288** | | |
| Isomer | No | **Racemic mix S+R enantiomers** | **Pure S-enantiomer** | |
| O:W PC | 2.9 | Hexanol:buffer coefficient = 28 | Hexanol:buffer coefficient = 2.9 | |
| Potency | | More potent than ropivacaine | Slightly less potent than bupivacaine | |
| Vasodilator? | | Yes – mild | No – vasoconstrictor properties | |
| Uses | Fast acting, short duration LA: topical/ regional/ neuraxial<br>VT as class 1B antiarrhythmic<br>4x less potent than bupivacaine | Slow acting, long duration amide LA | Slow acting, long duration amide LA | Fast acting, short duration amide LA for IV or as compound for EMLA |
| Pres | CCS 0.5-2% lignocaine hydrochloride (+/- 1:200 000 adrenaline) (↓solubility overcome by hydrochloride → buffered to pH 6)<br>Gel/ ointment / spray<br>Long shelf life | CCS racemic bupivicaine (S + R enantiomers) 0.25-0.5% +/- 1:200 000 adrenaline<br>heavy solution: 0.5% + 80mg/ml glucose<br>0.1% + 2microg/ml fentanyl | CCS racemic ropivacaine hydrochloride monohydrate (S + R enantiomers) 0.2/0.75/ 10mg/ml ropivacaine hydrochloride | CCS 0.5/1/2/4% prilocaine hydrochloride + 3% with 0.03IU felypressin/ml<br>Also in EMLA 5% 1:1 oil in water emusion |
| Action | Unbound, unionized fraction crosses lipid bilayer of axons → diffuses into axoplasm → becomes protonated + ionized → binds to voltage gated Na+ channels in their activated, open state → locks Na channel in inactivated-closed state → disrupts further neural transmission | | | |
| **CNS** | reversible neural blockade<br>biphasic effect:<br>- excitation: lightheaded, dizzy, visual + auditory disturbance, seizure → due to inhibition of inhibitory interneurone pathways in cortex<br>- ↑ doses: depression of facilitatory + inhibitory pathways occurs → CNS depression (drowsiness, disorientation, coma)<br>block neuromuscular transmission when administered intraneurally | | | |
| **CVS** | blockade of inactivated Na channels<br>- ↓phase IV cardiac AP depolarisation<br>- ↓AP duration<br>- ↓Refractory perior<br>- ↓conduction velocity<br>slight ↑SVR | cardiotoxic – binds to myocardial proteins → blocks cardiac Na channels + ↓rate of ↑ of phase 0 of cardiac AP<br>**Vasodilator** at low doses: Ad added | less cardiotoxic than bupivacaine;<br>in toxic conc → ↓PVR ↓myocardial contractility → ↓BP<br>biphasic vascular effect: **vasoconstriction** at ↓conc | Mild ↑SVR and MAP at low doses |
| **Resp** | Bronchodilation | Nil | Nil | |
| Toxicity/ SE | CVS: ↓PVR, ↓myocardial contractility → hypotension + possible cardiovasc collapse<br>RS: resp depression<br>Doses >600mg: methaemoglobinaemia due to metabolite O-toluidine | CNS: dose dependent excitatory effects (circumoral tingling, paraesthesia, twitching, confusion, seizure, ↓LOC, coma<br>CVS: ↓PVR ↓myocardial contractility → hypotension +/- cardiovasc collapse; affects K and Ca2+ channels<br>NB bupivacaine more cardiotoxic → binds to cardiac Na+ cannels + dissociates less easily | | **Methaemoglobinaemia** at doses >600mg |
| CNS: CVS | 7 | 3 | 5 | |
| Route/ dose | Topical/ infiltration/ intrathecal/ epidural<br>Max safe dose **3mg/kg** (7mg/kg with adrenaline)<br>Arrhythmia: 1mg/kg over 2 mins → infusion | Topical/ infiltration/ intrathecal/ epidural<br>Not for IV<br>**Max safe dose: 2mg/kg** (+/- adrenaline) | Not for spinal / IV<br>Topical / epidural/ infiltration<br>**Max safe dose 3mg/kg** (+/- adrenaline) | Max safe dose **6mg/kg** or 8mg/kg with adrenaline |
| Onset | 3min | <10-20mins | | |

| | | | | |
|---|---|---|---|---|
| Duration | 60-120min | 5-15hours | | |
| **A** | ↓lipid solubility, N-heptane buffer = 3 | ↑lipid solubility, N-heptane:buffer 27 | ↑lipid solubility, N-heptane:buffer = 9 | ↓lipid solubilty, N-heptane:buffer = 1 |
| pKa | 7.9 (weak base) | 8.1 (weak base) | 8.1 (weak base) | 7.9 (weak base) |
| %UI | 25% | 15% | 15% | 25% |
| **D** | VD 1L/kg | VD 1L/kg | VD = 1L/kg (→ intermediate lipid solubility) | VD 2.5L/kg |
| PB | **70% PB** (α1 acid glycoprotein) | 95% | 95% | 55% |
| **M** | **Liver**<br>N-dealkylation with hydrolysis to monoethylglycine (**MEGX**) + xylidide<br>**Active metabolites** (10% activity) | **Liver**<br>N-dealkylation → pipcolyloxylidine (**inactive**) | **Liver**<br>Aromatic hydroxylation via CYP450 to 3-hydroxylropivacaine (major metabolite), and 4 hydroxy-dealkylated-ropivacaine<br>**Active metabolites** | Liver + renal<br>Amidases → various metabolites including o-toluidine (→ **metHb**)<br>Not metabolised by plasma esterases |
| **E** | **Urinary** (<10% unchanged)<br>clearance 10ml/kg/min | Urine (15% unchanged)<br>Clearance 6ml/kg/min | 85% **urine** (1% unchanged)<br>Clearance 6ml/kg/min | Urine (inactive metabolites)<br>Clearance 30ml/kg/min |
| T1/2β | 90-120min | 30min | 2hr | 1hr |
| Special points | Metabolites may ↓seizure threshold<br>↓clearance in cardiac + hepatic failure | Adrenaline does not influence rate of systemic absorption as highly lipid soluble + direct vasodilatory effect<br>**Mixed S+R enantiomers → ↑toxicity + motor blockade, ↓potency** | Ideal epidural: ↓lipid solublity → penetration thick motor fibres (↑tendancy to block A-delta and C fibres → motor anaesthesia ↓intense/duration – good for obstetrics and post op pain) | |

*Esters*

| | **Procaine** | **Cocaine** | **Tetracaine (Amethocaine )** |
|---|---|---|---|
| Chem | 1st synthetic injectable LA of ester class | Ester of benzoic acid | Potent ester |
| Uses | LA, use now confined to infiltration anaesthesia | Topical vasoconstrictor (ENT/ nasal fibreoptic intubation) | Ophthalmology LA to eye |
| Pres | CCS 0.25/0.5-5% | Topical solution/ pastes 1-4% + moffats 2ml 8% + 2ml 1% sod bic + 1ml 1:1000 adrenaline | CCS amethocaine hydrochloride 0.5/1% |
| Action | As per amides | Blocks uptake of NAd and dopamine → vasoconstriction + CNS excitation<br>Also LA properties as per amides | |
| **CNS** | Low potency | Hyperreflexia, mydriasis, ↑IOP | |
| **CVS** | | Dose dependent:<br>- low: ↓HR due to ↑VA tone<br>- moderate: ↑BP, ↑HR (CNS stimulation + block NAd reuptake peripherally → intense peripheral vasoconstriction)<br>- large: myocardial depression; may precipitate VF and CC | |
| **Resp** | | Stimulates resp centre + ↑ventilation | |
| **AS** | | Hyperdynamic bowel sounds, N+V, ↑body temp | |
| **Other** | | | |
| Toxicity/ SE | | Acute cocaine toxicity:<br>- potent vasoconstriction → local ischaemia<br>- SY activity → ↑HR + HTN<br>- Sensitization to catecholamines → coronary vasospasm → precipitate ischaemia + MI<br>- Precipitate ventricular dysrhythmias<br>- Agitation + hyperpyrexia<br>- Seizures<br>- Foetal hypoxaemia (↓uterine blood flow)<br>Rx toxicity: GTN, IV BZDs ?esmolol | Local irritation/ burning/ stinging on instillation<br>Blurred vision, keratitis uncommon |
| Route/ dose | Max safe dose 8mg/kg | Max safedose 3mg/kg | Not for IV, spinal, epidural |
| Onset | Slow | Fast 15-30min | Very fast 10-20s |
| Duration | | | 10-20min |
| pKa | 8.9 (weak base) | 8.6 | 8.5 (weak base) |
| **A** | 3% unionized at pH7.4 (→ slow onset) | 5% unionized at pH 7.4 | |

| | | | |
|---|---|---|---|
| | low lipid solubility, N-heptane:buffer = 0.6 | well absorbed mucosa/ gut | |
| **D** | 6% PPB (α1 acid glycoprotein)<br>VD = 0.6Lkg | 98% PB<br>VD 2L/kg | |
| **M** | Plasma cholinesterase → para-aminobenzoic acid (PABA) | Plasma and hepatic esterases to norcaine (active) | Hydrolysed by plasma esterases (pseudocholinesterase) to para-aminobenzoic acid |
| **E** | Urinary<br>Clearance 60ml/kg/min<br>½ life 6mins | Urinary (10% unchanged)<br>Clearance 30ml/kg/min<br>½ life 40mins | Urine with unmetabolised drug |

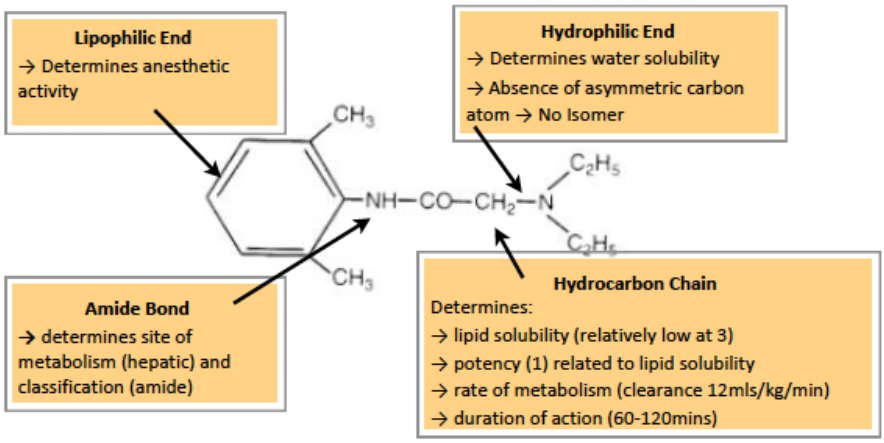
*Compare the pharmacology of ropivacaine and bupivacaine, and explain why ropivacaine may be considered a safer agent than bupivacaine: PAST QUESTION*

For comparison *see above*

***Reasons for ↑safety of ropivacaine***

| **Property** | **Mechanism** | **Ropivacaine** | **Bupivacaine** |
|---|---|---|---|
| Isomers | R enantiomer ↑lipid solubility + ↑toxicity | Pure S enantiomer | Racemix 1:1 mixture of R and S enantiomers |
| Lipid solubility | ↑lipid solubility → ↑uptake by CNS/CVS → ↑toxicity | Shorter propyl side chain, lower O:W 2.9 → ↓solubility | Longer butyl side chain, higher O:W 28 → ↑solubility |
| Vasoactivity | ↑Local vasodilation → ↑toxicity<br>↑Regional blood flow<br>↑systemic absorption<br>distribution to CNS + CVS | ↑vasoconstriction at low doses | ↑vasodilation at low doses (used with Ad) → ↑systemic absorption |
| Clearance | ↑systemic clearance → ↓toxicity<br>↓plasma concentration → ↓toxicity | Clearance 0.8L/min hepatic<br>T1/2 = 120mins | Clearance 0.5L/min hepatic<br>T1/2 = 160min |
| Cardiac receptor action | ↑affinity cardiac Na+ channels → ↑cardiotoxicity | Faster dissociation from cardiac Na channels → ↓toxicity<br>Duration of action → ↓ | Slower dissociation from cardiac Na+ channels → ↑toxicity<br>Duration of action → ↑ |

*Write brief notes on the physicochemical properties of lignocaine: PAST QUESTION*

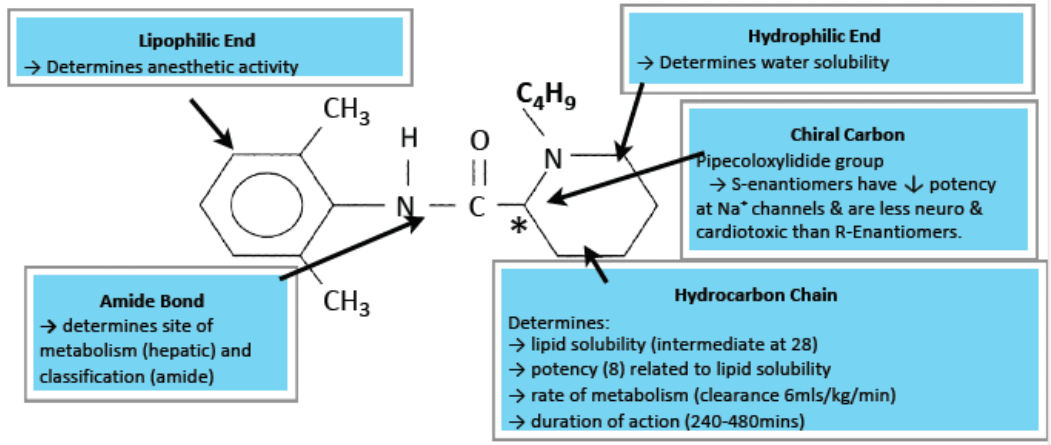



| Physichochemical property | | Result |
|---|---|---|
| Structure | Amide LA; Weak base | |
| MW | 234 | Similar to other LAs |
| pKa | 7.9 | 25% unionised at pH 7.4 → fast speed of onset |
| Lipid solubility | Hexanol:buffer coeff = 3 | 10x less soluble than bupivacaine → ↓potency<br>↓toxicity at given dose<br>able to ↑dose (↑vol + conc) → ↑speed of onset than bupivi |
| Protein binding | 70% plasma protein bound (1o α1 acid glycoprotein) | Duration of action 60-120mins<br>↓protein complexes formed at target site → ↑systemic absorption → ↑rate of metabolism |
| Intrinsic vasodilator activity | Low dose → vasodilate<br>High dose → vasoconstrict | ↑systemic absorption → ↓DoA<br>↓absorption by 1/3 with adrenaline |
| Isomerism | No | |
| Stable/ long shelf life | Yes – poorly water soluble so formulated as hydrochloride salt | Multiple preparations available: cream, gel 2%, ointment 5%, neb, aerosol, EMLA (2.5% + prilocaine), solution (0.5-2%), topical solution 4% |

*List the physicochemical characteristics of bupivacaine. Explain how they influence its pharmacodynamics effects at the site of administration: PAST QUESTION*

Bupivacaine = amide LA belonging to pipecoloxylidide group

- used for LA, peripheral nerve block, epidural/ intrathecal use
- poorly water soluble + presented as bupivacaine hydrochloride salts
- presented as CCS 0.25/0.5% with or without adrenaline and in heavy 0.5% solution with 80mg/ml glucose for intrathecal use
- low CVS:CNS ratio (3) → most cardiotoxic due to ↑lipid solubility + receptor affinity




| Physichochemical property | | Result |
|---|---|---|
| Structure | Amide LA; Weak base | |
| MW | 288 | Not suitable for topical administration |
| pKa | 8.1 | 15% unionised at pH 7.4<br>medium onset of action<br>↓pH in site (infection) → ↓unionised portion |
| Lipid solubility | Hexanol:buffer coeff = 27 | ↑potency as take up by tissues quickly → ↑toxicity risk for a given dose<br>smaller dose (↓conc, vol) given → ↓speed of onset cf lignocaine (Bowman principle) |
| Protein binding | 95% plasma protein bound (1o α1 acid glycoprotein) | Duration of action 240-4800mins<br>protein complexes formed at target site<br>↑free drug in pregnancy (PG binds α1AG) |
| Intrinsic vasodilator activity | More vasodilation than ropivavaine (less than lignocaine) | ↑systemic absorption → ↓DoA<br>adrenaline has mild effect |
| Isomerism | Racemix mixture 1:1 R and S enantiomers | R enantiomer associated with ↑toxic SE (↑lipid solubility and efficacy → ↑cardiotoxic) → ↑risk of toxicity cf levo-bupivacaine |

*20mls of 0.5% bupivacaine is inadvertently administered IV over 15seconds to a 60yr old 60kg woman. Describe the potential complications and mechanisms of these*

**Describes a life-threatening medical emergency**
Potential complications = cardiovascular + CNS toxicity

***Background***
- bupivacaine = long acting amide LA
- dose limit for nerve block = 2mg/kg
- plasma [bupivi] threshold for CNS toxicity ~2mg/L
- plasma [bupivi] thresho for CVS toxicity ~6mg/L
- this refers to the total [bupivi] i.e. both protein bound + unbound forms

Patient was administered:
5mg/ml bupiv x 20ml = 100mg IV
60kg, blood vol = 60 x 70 = ~4L
therefore expected total plasma [bupivi] = 100mg/4L = 25mg/L
Exceeds thresholf for CNS and CVS toxicity → pt at risk of life-threatening LA toxicity if not managed

***Mechanism of toxicity***
- Bupivi = LA; tightly binds and inhibits action of all excitable tissues (nerves, myocardium) via blocking voltage gated (fast) Na+ channels
- Unionised, unbound bupivi molecule diffuses across cell membrane → becomes ionised and binds to VG Na+ channels + locks it in open inactivated state → prevent further depolarisation
- **CNS toxicity**
  - When VG Na+ channels are blocked, neuronal transmission is disrupted. In CNS →
  - Blocked BS CN nuclei → tinnitus, altered taste, perioral numbness
  - Blocked inhibitory neurones → seizures
  - Blocked ascending arousal pathways → ↓LOC + coma
  - Blocked BS centres → resp depression
  - Blocked motor nerves → weakness
- **CVS toxicity**
  - When VG Na+ channels of myocardium are blocked →
  - Blocked conduction pathway → ventricular bradyarrhythmias + tachyarrhythmias (classically refractory VT/VF)
  - Blocked myocardium → ↓contractility + thus CO
  - Blocked vascular smooth muscle → vasodilation + venodilation
  - Blocked cardioaccelerator plexus (T1-T4) + medullary vasomotor centre → unable to compensate + cardiovascular collapse
  - Furthermore → ↓CO prevents removal of bupic from myocardium + nerves → further prolong effect

***CC:CNS ratio***
- Usually onset CNS toxicity lower plasma concentration than onset of CVS toxicity
- CC:CNS ratio = ratio of LA dose that results in cardiovascular collapse (CC) to dose that results in CNS toxicity
- LA with higher CC:CNS ratio are deemed safer as more CNS symptoms as warning prior to onset of CC
- CC:CNS ratio for
  - Bupivacaine = 3
  - Ropivavaine = 4
  - Lignocaine = 7

*Factors which increase the risk of systemic toxicity with amide LA agents: PAST QUESTION*

***Background***
- LA = drugs that reversibly inhibit transmission of neural impulses in the applied region, without affecting consciousness
- Amide LAs = subgroup of LAs where the lipophilic aromatic ring + hydrophilic terminal amine are linked by amide group

**LA toxicity**
- systemic toxicity of amide LA = due to excess plasma concentrations
- accidental direct IV injection = most common cause
- toxicity include:
  - CNS toxicity: excitatory (perioral numbness, tinnitus, visual disturbances, seizures); inhibitory (sedation, resp depression, coma)
  - CVS toxicity: arrhythmias (ectopics, conduction block, refractory VT/VF), hypotension, CC
  - Other toxicity: methaemoglobinaemia (prilocaine)
- Examples of amide LAs and max safe doses

| LA | Maximum safe dose (mg/kg) | CNS/CVS ratio |
|---|---|---|
| Lignocaine | 3 without adrenaline<br>7 with adrenaline | 7 |
| Ropivacaine | 3 | 4 |
| Bupivavaine | 2 | 3 |
| Prilocaine | 6 | |

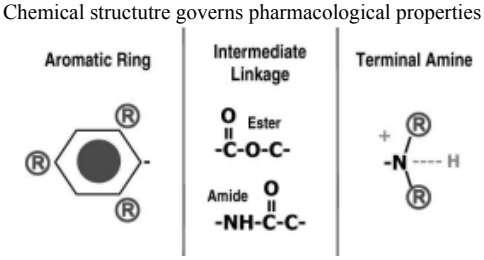
***Factors that govern the risk of toxicity include:***
- **Drug factors:**
  - **A:**
    - Rate of absorption into systemic circulation = governed by Fick's law of diffusion
    - $$\text{Rate of diffusion} = \frac{area}{thickness} \times \frac{sol}{\sqrt{MW}} \times conc\ gradient$$
      - Surface area: ↑injected vol (esp. epidural) → ↑contact surface area → ↑rate of diffusion → ↑risk toxicity
      - Thickness: ↓diffusion distance → ↑rate of diffusion e.g. proximity to vessels: intercostal <epidural < brachial plexus
      - solubility: ↑lipid solubility → ↑rate of diffusion → ↑risk toxicity
      - ↑concentration gradient
        - ↑dose → ↑concentration gradient → ↑rate of diffusion → ↑risk of toxicity
        - ↑blood flow → maintains conc gradient by washing away absorbed LA

        - ↓local blood flow (i.e. addition of adrenaline) → ↓rate of absorption → ↓toxicity
    - **D**
        - Protein binding
            - ↑PB → ↑DoA → ↓systemic availability → ↓risk toxicity
            - however, in event of toxicity, ↑PB → ↑duration of toxicity
        - Lipid solubility
            - ↑lipid solubility → ↑penetration into CNS + cardiac cells → ↑risk toxicity
            - egbupvavaine 30x more lipid soluble cf lignocaine
        - pKa
            - all amide LAs are basic → lower pKa → ↑unionised fraction → ↑systemic absorption = ↑risk toxicity
            - ↑pKa → ↑prone to trapping in acidic environments → ↑risk toxicity
    - **M+E**
        - Amides metabolised by liver (amidases) into less active metabolites
        - Metabolism slower than ester LAs
        - Hepatic dysfunction → ↓rate metabolism → ↑risk toxicity
    - **Pharmacodynamics:**
        - optical isomerism → impact potency → R-enantiomer more potent than S-enantiomer
        - CVS:CNS ratio = ratio of the dose causing CC to the dose causing seizures
            - Lower the number = ↑cardiotoxic the drug
            - e.g. bupicavaine has lower CVS:CNS ratio cf lignocaine → more likely to produce cardiotoxicity
- **Patient factors**
    - **Weight**, age, comorbidities
    - **Acidosis**: Amides protonated + ionised in acidic environments → intracellular ion trapping → toxicity
    - **VD**: ↓VD → same dose produces ↑plasma concentration → ↑risk toxicity.
    - **↑patient weight** → ↑VD → ↓risk toxicity
    - **↑age** → ↓VD + myocardium ↑sensitivity to LA
    - **pregancny** → ↑senstivitiy to LA ?progesterone related
    - **cardiac** disease: can result in ↓VD, hypoperfusion, acidosis
    - co-administered drugs
- Drug interactions
    - Competition for protein binding AAG

## *Describe how the chemical structure of local anaesthetic drugs determines their efficacy and safety: PAST QUESTION **NB CORE MATERIAL***

Background
- LA = drug which reversibly prevents transmission of nerve impulse in the region to which it is applied, without affecting consciousness
- Efficacy (or intrinsic activity) = measure of the magnitude of effect once drug is bound
- Safety = relationship between dose of drug required to produce desired + undesired effects
    - With LAs: toxicity ratio CVS:CNS is used as a measure of safety and compares plasma conc required to produce CNS side effects (reversible, treatable) to onset of CVS symptoms (CC)

**Chemical structure of LAs**
- Typical chemical structure of LA = lipophilic aromatic ring, intermediate linkage (either amide or ester) and hydrophilic amine tail
- Chemical structutre governs pharmacological properties of La → and therefore efficacy + safety profile

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***Structure activity relationships***
- **lipophilic aromatic ring**
    - substituents can alter lipophilicity of LA
    - ↑lipophilic substituents → ↑lipophilicity + ↑protein binding → more potent + longer duration of action
    - e.g. procaine has amine group; tetracaine has butyl group → tetracaine lipophilic > procaine
- **intermediate linkage**
    - ester linage rapidly metabolised by plasma esterases: ↑risk allergy but ↓risk systemic toxicity due to ↓DoA
    - amide linkage metabolised by liver: ↑risk toxicity due to ↑DoA
- **hydrophilic amine tail**
    - substituents on hydrophilic amine tail can alter lipophilicity of LA
    - ↑lipophilic substituents → ↑lipophilicity + ↑PB → ↑potent + longer DoA
    - e.g. mepivavaine has methyl substituent on amine tail, bupivacaine has butyl → bup 35x more lipophilic than mepivavaine
- **Chirality**
    - Na+ channel ion is chiral → interaction between LA + Na+ channel demonstrates stereoselectivity
    - E.g. R-dextrobupivacaine ↑potent than S-levobupivacaine → ↑toxicity R bupiv cf S-bupiv

***Toxicity profile***
degree of LA toxicity related to:
- **plasma concentration**
    - faster rate of metabolism → ↓peak [LA] → ↓toxicity
    - e.g. esters undergo rapid metabolism → less toxic cf amides
- **LA potentcy**
    - ↑hydrocarbon length of intermediate linkage →↑lipophilicity → ↑potency → ↑toxicity
    - lipophilic substituents on lipophilic aromatic ring + hydrophilic amine tail → ↑lipophilicity → ↑potency → ↑toxicity
- **Duration of action**

- ↑lipophilic substituents → ↑PB + ↑lipophilicity → ↑DoA → ↑toxicity
- **Metabolites**
  - Esters metabolised to p-aminobenzoic acid derivatives → ↑risk hypersensitivity

## *Describe the factors that determine skin penetration of local anaesthetics. Describe the formulation and pharmacology of EMLA: PAST QUESTION*

***Background***

- LA = drug which reversible inhibits transmission of nerve impulses in the applied region, without affecting consciousness
- Can be applied topically to block dermal pain + sensory nerves → facilitate painful transcutaneous procedures
- Need to diffuse through skin layers to reach target nerve fibre
  - 5 sublayers of epidermis: stratum corneum → lucidum → granulosum → spinosum → basale
  - dermis: containing nerve endings + fibres + blood vessels

***Factors determining onset of topical LAs***

- governed by Fick's law of diffusion
  - $$\text{Rate of diffusion} = \frac{area}{thickness} \times \frac{sol}{\sqrt{MW}} \times conc\ gradient$$
  - Area: ↑applied area → ↑contact surface area → ↑rate of diffusion → faster onset
  - Thickness: ↑thickness → ↑diffusion distance → ↓rate of diffusion
  - Lipid solubility
    - LAs need to cross lipid bilayers to reach target nerve fibre in dermis: ↑lipid solubility → ↑rate of diffusion → faster onset
    - Lipid solubility depends on intrinsic properties of LA + pKa (and thus, unionised fraction)
    - LAs = generally basic → ↓pKa → ↑unionised fraction → ↑lipid solibilty → ↑onset
    - E.g. oil:water partition coefficient of lignocaine = 2.9; prilocaine =0.9
  - Molecular weight: ↑MW → ↓rate of diffusion
  - Concentration gradient: ↑dose → ↑conc gradient → ↑rate of diffusion → faster onset

***Topical LAs and EMLA***

- most commonly used topical LAs = EMLA + amethocaine
- EMLA = eutectic mixture of local anaesthetics
- eutectic mix = combination of 2 or more substances → resulting combination melts as a whole at specific temp i.e. the mixture of constituents at a ratio that produces the lowest termperature melting point
- Formulation
  - 5% white emulsion containing:
    - 2.5% lignocaine
    - 2.5% prilocaine
    - polyoxyethene fatty acid ester (emulsifier)
    - carbopol (thickening agent)
    - sodium hydroxide (adjusted to pH 9)
    - water
  - melting point of lignocaine = 67oC, prilocaine = 37oc, EMLA = 16oC
- Application
  - 1-2g EMLA applied per 10cm2 area of skin then occlusive dressive applied
  - wait 30-60min before venepuncture/ cannulation
  - initially causes local vasoconstriction → may cause vasodilation after 60-120mins
- Toxicity
  - Local reactions
    - Avoid on broken skin, mucosal surfaces , infected tissue
    - Not for use in infants <3 months
  - Hypersensitivity
  - Systemic absorption
    - Avoid in pts an antiarrhythmics → possible additive/synergistic effects
    - Prilocaine metabolised to o-toluidine → oxidises Fe2+ of haeme moiety to Fe3+ → may precipitate methaemoglobinaemia → hypoxia
- EMLA has significantly ↑cutaneous diffusion due to:
  - Eutectic mixture → lower melting point → lignocaine + prilocaine mixture exists in liquid form → allows ↑conc to be used (which would otherwise precipitate in solution) → ↑diffusion
  - Eutectic mixture → liquid form → allows buffer to alkaline pH (without precipitation) → ↑unionised fraction → ↑lipid solubilty → ↑diffusion

## *Describe the required (ideal) pharmacological characteristics of LA formulations intended for topical use: PAST QUESTION*

General:

- LAs = agent which block neuronal impulses by blockage of Na channels on neuronal axons → prevent the propagation of APs
- Classified into Amide and Ester LAs

Topical use

- application of agent to external surface in order to achieve blockade
- epithelial (skin) or mucsal
- obeys Fick's law of diffusion
  - $$\text{Rate of diffusion} = \frac{area}{thickness} \times \frac{sol}{\sqrt{MW}} \times conc\ gradient$$

***Ideal characteristics***

- Physicochemical
  - Water soluble
  - Variety of formulations to assist clinical applications: cream, gel, ointment, aerosol, lozenge, drops → depending on site of intended action
  - Long shelf life
  - Stability during storage
  - No additives/ preservatives
  - Easy + economic production
- Pharmacodynamic

- Effective block of nerve transmission
- acts on dermal fibres when applied topically
- High CVS:CNS ratio or high therapeutic ratio with minimal or no neurotoxicity or cardiotoxicity
- inltrinsic vasoconstrictor properties: ↓systemic absorption → ↑DoA; minimise blood loss
- No local site irritation
- No ability to oxidise Hb to form metHb
- Does not cross placenta

- Pharmacokinetic
  - Absorption
    - Concentration of active component
    - Buffers: ↑unionised portion → ↑lipid solubility → ↑absorption
    - Low melting point → ↑solubility
    - Low MW → ↑rate of diffusion
    - pKa close to 7.4 (maximal unionised fraction at physiological pH)
    - lipid soluble → ↑uptake
    - intrinsic vasoconstrictor activity → ↓systemic absorption → ↑duration of action/ time at target site
  - Distribution: ↑PB → ↓VD → ↑duration of action + time at target site
  - Metabolism: ↓metabolism → ↑DoA, high systemic clearance → ↓toxicity
  - elimination by urine only of metabolites; no active/ toxic metabolites

## *Outline the toxicity of local anaesthetics: PAST QUESTION*

***Background***

- toxicity = unwanted harmful effect of a drug
- LA= drugs that reversibly inhibit transmission of neural impulses in the applied region without affecting consciousness
- Toxicity from LA can be classified into local or systemic
  - Local toxicity: mechanism of delivery + reaction to PABA
  - Systemic toxicity = due to excess plasma concentration determined by rate of drug entrance relative to its redistribution and clearance by metabolism

***Maximum recommended doses:***

| | **Dose in mg/kg** | **Toxic plasma levels** | **CC:CNS ratio** |
|---|---|---|---|
| Lignocaine | 3mg/kg without adrenaline<br>7mg/kg with adrenaline | >5microg/ml | 7 |
| Bupivacaine | 2mg/kg up to 140mg +/- adrenaline | >1.5microg/ml | 3 |
| Ropivacaine | 3mg/kg +/- adrenaline | >4microg/ml | 5 |

***Local toxicity***

- **High epidural or spinal blockade**
  - β fibres = small myelinated fibres readily blocked by LAs
  - large doses of epidural/spinal LA can result in inappropriately high block
  - High SY chain block
    - Vaso+ veno dilation → ↓SVR + ↑venous capacitance → ↓↓MAP
    - Venodilation → ↓VR → ↓RAP → ↓HR
    - Blockade of cardioaccelerator (T1-T4) fibres → ↓↓HR
  - Brainstem block
    - Blockade of resp centre → profound resp depression
    - Blockade of autonomic centre → CVS collapse (↓↓MAP + ↓↓HR)
- **Neurotoxicity**
  - epidural/ intrathecal injection → neurotoxicity: mechanism: lignocaine ↑intracellular [Ca2+] → neurotoxic via unknown mechanism
  - radicular irritation → transient neurological symptoms that resolve over 1-7days
  - cauda equina syndrome → diffuse lumbosacral plexus injury → sensory, bladder + bowel dysfunction, paraparesis
  - anterior spinal artery syndrome → lowe limb paresis + dysaesthesia ?2° anterior spinal artery spasm

***Systemic toxicity***

- **CNS toxicity**
  - Biphasic effect
    - Excitatory phenomena: depression of inhibitory interneurons → circumoral tingling, tongue numbness → restlessness, tinnitus, vertigo → skeletal + facial muscle twitching → seizure
    - CNS depression: depression of central neurons → coma, apnoea
  - Seizure ?2o inhibition of inhibitory GABAergic pathways → unopposed excitatory activities → seizure
- **CVS toxicity**
  - ↑↑dose reuired to produce CVS toxicity than CNS toxicity
  - Main effects: hypotension + bradyarrhythmias
  - Mechanism:
    - Cardiac Na channel blockade LAs → slow conduction of cardiac impulses → PR prolongation + QRS widening → VTs
    - Inhibit Ca2+ and K+ ion channels
    - Inhibit cAMP synthesis (minor)
    - Relaxation of arteriolar vascular smooth muscle
  - CC:CNS ratio: ratio of the dose required to cause CVS collapse and the dose required to cause CNS toxicity: indicates that CNS is ↑vulnerable to LA than CVS
- **Hypersensitivity reaction**
  - Rare
  - LA or additive can → hypersensitivity reaction
  - Ester LAs metabolised to para-aminobenzoate (↑rates allergy)
- **Hepatotoxicity**
  - Continuous epidural infusion of bupivacaine found to rarely cause hepatic enzyme derangement + hepatoxcicity
  - Mechanism unclear
- **Methaemoglobinaemia**
  - Prilocaine metabolised in liver to o-toluidine → oxidises Fe2+ of haem to Fe3+ → ↑methaemoglobin (unable to carry O2) → tissue hypoxia

**Ester vs. amide toxicity**

***Cocaine toxicity (ester)***

Acute cocaine toxicity:

- potent vasoconstriction → local ischaemia
- SY activity → ↑HR + HTN
- Sensitization to catecholamines → coronary vasospasm → precipitate ischaemia + MI
- Precipitate ventricular dysrhythmias
- Agitation + hyperpyrexia
- Seizures
- Foetal hypoxaemia (↓uterine blood flow)
- Rx toxicity: GTN, IV BZDs ?esmolol

***Dose dependent effects of lignocaine toxicity (amide)***

| Dose (ug/mL) | CNS Toxicity | CVS Toxicity |
|---|---|---|
| 1 ~ 5 | Minimal toxic effects | Slight ↓cardiac automaticity |
| 5 ~ 10 | circumoral numbness<br>tinnitus<br>skeletal muscle twitching | hypotension<br>myocardial depression |
| 10 ~ 15 | seizures<br>↓LOC | |
| 15 ~ 25 | apnoea<br>coma | |
| > 25 | | cardiovascular collapse |

*(Table from Stoelting 5th ed pg 293)*

***Factors affecting risk of toxicity***

- Drug factors
  - Dose
  - Route + location of administration
  - Potency; pKa
  - Isomerism (R-enantiomer more toxic than S)
  - Rate of metabolism
  - PB (↑PB → ↓free drug → ↓toxicity)
  - Intrinsic vasodilator activity
- Patient factors
  - Acidosis → ↑ionised → ion trapping → ↑toxicity
  - Pregnancy → ↑progesterone → competitive binding to AAG → ↑unbound LA → ↑toxicity
  - Hepatic/renal dysfunction
  - Heart failure → ↓perfusion + ↓VD → ↓elimination
  - Plasma cholinesterase activity

***Prevention of LA toxicity***

- Frequent aspirations
- Slow injection
- Test dose
- Total dose administered < max recommended dose
- Awake patient
- Monitoring
- USS guided
- Vasoconstrictors

*Management of local anaesthetic toxicity: MAKEUP*

***Management of severe LA toxicity***

- Recognition
  - Sudden alteration in mental status/ agitation/ LOC/ seizures
  - CC: sinus brady, conduction blocks, asystole, ventricular tachyarrhythmias
- Immediate management
  - Stop injecting
  - Call for help
  - Maintain airway
  - ABCD
  - 100% O2 NB hyperventilation may help by ↑plasma pH
  - IV access
  - Control seizures
- Treatment
  - Circulatory arrest: CPR + IV 20% lipid emulsion 1.5ml/kg over 1min and start infusion at 15ml/kg/hr. Max 2 boluse. Can double infusion rate to 30ml/kg/hr after 5 mins if ongoing cardiovascular stability or deterioration. Continue until stable or max dose given (max 12ml/kg)
  - No circulatory arrest: conventional therapies to hypotension, bradycardia, tachyarrhythmia (don't use lignocaine as antiarrhythmic)

*A surgeon wishes to use topical anaesthetic in the nose before surgery in a 30 year old 70 kg man. He normally uses topical cocaine 5% plus lignocaine 2% with adrenaline 1: 100,000 injection. What volumes of cocaine 5% and lignocaine can be used safely? What are the potential toxic effects of cocaine and how do lignocaine and adrenaline affect this? PAST QUESTION*

| | COCAINE | LIGNOCAINE | ADRENALINE |
|---|---|---|---|
| Description | *Ester of benzoic acid*<br>Used as topical local anaesthetic & vasoconstrictor | *Amide* & *type 1B antiarrhythmic*<br>Used as topical, infiltrative & epidural local anaesthetic | *Catecholamine*<br>Used with local anaesthetics due to its potent vasoconstrictor properties |
| Toxic Doses | 3mg/kg | 3mg/kg plain<br>7mg/kg with adrenaline | |
| Case Dose Amount | 5% = 50mg/mL | 2% = 20mg/mL | 1:100,000 = 10mcg/mL |
| Case Dose Safety | Maximum dose for 70kg = 3 x 70 = 210mg → 4.2mL<br><br>Toxicity is additive therefore 50% ≈ 2 mL | Maximum dose for 70kg = 7x70 = 490mg → 24.5mL<br><br>Toxicity is additive therefore 50% ≈ 12 mL | 12 mL lignocaine + Ad ≈ 120 mcg Ad → This is a significant dose when systemically absorbed |
| *Cocaine Pharmacology* | | | |
| Mechanism of Action | 1. **Blocks $Na^+$ channels** in frequency dependent manner → Prevents depolarisation & propagation of AP<br>2. **Blocks reuptake of NAd, DA & 5HT** via inhibition of reuptake-1 pathway → ↑ Monoamine levels at CNS synapses → Vasoconstriction & CNS excitation | | |
| Toxicity | 1. **Potent vasoconstriction:**<br>a. Local ischaemia (Eg. nasal mucosa)<br>b. Coronary vasospasm → Precipitate myocardial ischaemia/infarction<br>2. **Sympathomimetic activity** → ↑HR + ↑BP<br>a. ↑ Myocardial $O_2$ requirements + ↓ coronary blood flow 2° vasospasm → Precipitate myocardial ischaemia<br>3. **Sensitisation to catecholamines** → Ventricular tachyarrhythmias (VF/VT)<br>a. Facilitated by concurrent use of Ad or halothane<br>4. **CNS excitation** → Euphoria, agitation, delirium in elderly → Drug of abuse<br>5. **Hyperpyrexia** → Seizures<br>6. Dose dependent **↓ uterine blood flow** → Foetal hypoxia & acidosis | | |
| Treatment of Cocaine Toxicity | 1. **GTN & Nitroprusside:** for myocardial ischaemia & hypertension<br>2. **β-Blockers (esmolol):** recommended for tachycardia however may accentuate coronary artery spasm + trigger cardiovascular collapse<br>3. **α-Blockers:** for coronary vasoconstriction<br>4. **Benzodiazepines:** for seizures | | |
| Combination with Lig+Adr | 1. Lignocaine → Enhances CNS toxicity + CVS arrhythmias<br>2. Adrenaline → Enhances CVS vasospasm + arrhythmias + LOCAL nasal mucosal ischaemia | | |

## Describe the pain and sensory pathways

*See Neurophysiology Section*

## Describe the principles of ultrasound imaging and the safe use of ultrasound equipment for regional anaesthesia

USS

- Uses piezoelectric effect to produce images from pulsed sound waves of 1-20MHz (>limit human hearing)
- Piezoelectric effect occurs when crystals are deformed by passage of electrical current + produce electrical potential in response to physical compression
- Send + receive pressure waves in form of USS
- USS transducer = transmitter + receiver
    - Length of time between transmitting + receiving signal = tissue depth that signal reflected from
    - Strength of returning signal indicates amount of reflected waves = density of medium i.e. bone + air = totally reflect USS beam → shadowing
    - ↑frequency = ↑resolution but ↓penetration

In plane + out of plane

- In plane technique: USS probe held parallel to needle → entire shaft of needle visible
- Out of plane technique: USS bean perpendicular to needle → cross section of needle visible as small white dot

Advantages

- Accelerate block onset, ↑success rate, ↓dose of LA used, ↓time take to perform, ↓incidence of complications (e.g. vascular puncturez)

## Describe the principles of nerve stimulation to locate nerves and the safe use of nerve stimulators

**Peripheral nerve stimulator**

- Used if no USS or in combination with USS
- Production of evoked muscle contractions at low current levels (0.2-0.5mA) = confirm placement of needle in close proximity to nerve
- Production of evoked contractions at very low current thresholds (<0.2mA) = likely itraneural needle tip placement
- Using the nerve stimulator
    - Start with current 1.5mA and frequency 1-2Hz
    - Stimulus duration 0.1ms should preferentially stimulate motor nerves rather than sensory
    - Insert insulated needle + move in small steps <1-2mm
    - Aspirate then inject 1ml LA → motor response should disappear as nerve is displaced by fluid. If doesn't then ?needle in nerve sheath → reposition
    - If any pain or ↑resistance → ?in nerve → reposition

# Regional anaesthesia – other

**Continous regional anaesthesia: MAKEUP**

CRA:

- catheter placed near a nerve or plexus → LA injected or infused down catheter for hours –days postop
- early mobilisation; ↑analgesia
- prone to dislodgement
- sites: interscalene, supraclavicular, infraclavicular, paravertebral (trunk); post lumbar plexus, sciatic, femoral, popliteal

## *Outline the factors which would make a local anaesthetic agent suitable for use in obstetric practice: PAST QUESTION*

***Maternal considerations***

- ↑speed of onset of conduction blockade
- ↑susceptibility to LA toxicity (↑progesterone → ↑tissue sentivity + ↓PB → ↑free fraction)
- ↓dose required in spinal/ epidural due to engorged epidural vascular plexus
- Factors improving LA use in mother:
    - Degree of cardiotoxicity
        - Bupivacaine = ↑cardiotoxic than ropivacaine
        - Bupivacaine toxicity ↑in pregnancy: CC:CNS ratio ↓from 3 to 2 in pregnancy = unsafe
    - Degree of CNS toxicity
    - Motor function preserved: ropivacaine affects Adelta + C fibres > motor fibres → better
    - Method of metabolism: esters metabolised by plasma esterases which ↑in pregnancy

***Foetal considerations***

- ↓plasma PB → ↑free fraction which can cross into the foetal circulation
- foetal pH lower than in maternal circulation → ion trapping of LA as proportion of drug in charged form is ↑ → less easy to travel back into maternal circulation → ↑toxicity. Effect exaggerated if foetal distress + acidosis
- factors affecting LA choice in baby
    - degree of placental transfer
        - ↑PB → ↓drug in free form → ↓placental transfer; e.g. bupivi and ropivi PB95% = lower foetal:maternal ratio (0.32) than lignocaine 0.73
    - possibility for methaemoglobinaemia: prilocaine metabolite o-toluidine
    - factors affecting systemic absorption:
        - epidural/ intrathecal safer than intercostal
        - systemic absorption: intercostals > caudal > epidural > brachial plexus > subcut
        - ↑dose → ↑absorption

***Normal practice in obstetrics***

- ropivacaine preferred agent for epidurals: relative sparing of motor block; low foetal:maternal ratio, ↓risk toxicity
- bupivacaine good for intrathecal route

# CENTRAL NEURAXIAL BLOCKS

## Central neuraxial blocks in general: MAKEUP

| | **Spinal** | **Epidural** |
|---|---|---|
| Indications | lower abdo / perineal surg; LE; LSCS | abdo, LE, LSCS, NB due to segmental nature, may be suboptimal for sacral distribution |
| Details | Spinal anaesthesia is injected into subarachnoid space and blocks small, unmyelinated SY fibres then myelinated sensory + motor NB: | Main site of action = nerve roots<br>To lesser extent analgesia provided by diffusion into subarachnoid space |
| Anatomy | LA +/- adjunct injected into subarachnoid space<br>Subarachnoid space: extends laterally along the nerve roots to the dorsal root ganglia; continuous with intracranial subarachnoid space | LA +/- adjunct injected in epidural space<br>Epidural space = potential low pressure space that lies between the walls of the vertebral canal + spinal dura mater |
| Injection location | Lumbar only | Anywhere |
| Duration of block | Brief | Prolonged |
| Procedure time | Brief | Longer |
| Quality of block | High | Not as good as spinal |
| Factors influencing spread | act directly on SC; all modalities below upper limit of block affected<br>SY block can exceed motor/sensory by 2 dermatomes<br>Always blocks down to sacral levels<br>↑reliably affects both sides of body<br>**Seated:** saddle block → no higher than upper L levels → pelvic OT, spares ventilation<br>**Supine:** LA pools ~T3 → lower abdo OT<br>Hyperbaric solutions: glucose → ↑gravity<br>Variability of spread ↑with isobaric | LA spread in cranial + caudal directions from level administered<br>LA bathes nerve roots passing through anterolateral epidural space<br>Roots above + below limit spread → top + bottom level of effect<br>May be preferential spread to one side → different level + intensity of blockade on each side of body<br>Patchy block: single nerve roots missed |
| Intensity of blockade | Intensity of block related to **dose** of LA (dose = vol x conc)<br>Addition of opioids → ↑sensory blockade without affecting motor | Intensity of block ∝ **concentration** of LA<br>Addition of opioids → ↑sensory blockade without affecting motor |
| Advantages | Ability to produce segmental block<br>Greater control over analgesia<br>Possibility of long term analgesia<br>Profound NMB occurs with neuraxial anaesthesia – obviating the need for NMBDs | |
| Contraindications | Relative:<br>- aortic/ MV stenosis (↓BP 2o SY block)<br>- hypovolaemia (↓BP)<br>- previous back surgery<br>- neuro disease: ↑ICP<br>- systemic sepsis (↑risk abscess/ meningitis)<br>- platelets <80<br>Absolute<br>- patient refusal<br>- LA allergy<br>- Local sepsis<br>- Anticoagulation | |
| Agents used | **Bupivacaine** e.g. heavy bupivacaine: 0.5% + 8% glucose | **Bupivacaine** 0.125/ 0.25% +/- fentanyl 2microg/ml<br>**Levobupivacaine** 0.125% and 0.0625%<br>**ropivocaine** 0.2% with fentanyl 2microg/ml as premix solution<br>**lignocaine** |
| Complications | Common immediate:<br>- failure/ incomplete block<br>- hypotension<br>- N+V 2o hypotension<br>- Shivering/ itching<br>- Temporary backache<br>Uncommon immediate<br>- bradycardia 2o block of SY supply to heart<br>- impairment of accessory muscles of respiration<br>- horners syndrome if stellate ganglion involved<br>- phrenic nerve paralysis if C3-5 roots involved<br>- CN palsies<br>Uncommon late<br>- dural tap headache<br>- urinary retention<br>- neurological damage 2o direct trauma/ epidural haematoma/ spinal cord ischaemia<br>- epidural abscess / meningitis / arachnoiditis<br>- Permanent injury 1:25 000-1:50 000 | |

Combination low dose subarachnoid LA +/- opioid + top ups of weak epidural LA → rapid onset with minimal motor block
NB: Anything above T5 inhibits SNS to GIT

***Timing of anaesthesia***

- first 5-10mins critical re monitoring CVS response + level
- temp changes = 1st to go
- Sensory level + type of surgery
  - S2-5: haemorrhoidectomy
  - L2-L3: foot surgery
  - L1-3 lower extremity
  - T10: hip, TURP, vaginal delivery
  - T6-7 lower abdo, appendicectomy
  - T4: upper abdo, LSCS

*Central neuraxial analgesia and anticoagulants: MAKEUP*

- Aspirin and NSAIDs
  - No contraindications
- Clopidogrel
  - Stop 7 days before neuraxial block
- UFH:
  - Subcut VTE
    - doses seldom associated wit bleeding and not considered to ↑risk of vertebral canal haematoma significantly
    - wait 4 hours before or give >1hr post block
  - IV
    - Therapeutic anticoagulation with heparin = contraindication to regional block
    - Discontinue infusion for 4hrs + APTT normal before attempting block or removing catheter or give >1hr post block
- LMWH
  - Longer ½ lives than UFH
  - Fibrinolytic + anti Xa activity
  - For VTE prophylaxis: wait at least 12hrs before central neuraxial block/ catheter removal or give >2hrs post
  - If high dose LMWH for therapeutic anticoagulation: takes 24hrs for coags to return to normal
- Warfarin
  - INR 1.5 or less – usually takes 4 days
  - Consider LMWH until warfarin re-established

## Describe factors influencing dose and choice of anaesthetic agents for spinal anaesthesia and epidural anaesthesia/analgesia

**Background**

LA:

- drugs that reversibly inhibit transmission of neural impulses in the applied region without affecting consciousness
- MoA: block Na channels on inside of axonal membrane → preventing depolarisation + conduction along nerve
- Affect all nerve fibres; ↑effect on small unmyelinated axons
- Low dose: analgesia + peripheral vasodilation via Adelta (pain, temp, touch) + B(preganglionic, autonomic) fibres; less effect on somatic muscle activity mediated by large myelinated Aa (motor, proprioception) and A-gamma (motor to muscle spindles) fibres
- Higher concentration: block all nerve modalities

***Dose of LA***

- Dose = concentration x volume
- Depends on age + pregnancy: older patients/ pregnant → ↓dose
- Maximum safe dose varies between agents

***Choice of agent***

- Depends on:
  - Drug factors: i.e. licenced for epidural or spinal; duration of analgesia desired
  - Surgical factors: type of surgery i.e. long or short
  - Patient factors: allergies / pregnancy
- ***epidural***
  - Most common epidural solution: ropivocaine 0.2% with fentanyl 2microg/ml as premix solution
  - Initiation of analgesia
    - Bupivacaine 0.125% and 0.25% +/- fentanyl 5microg/ml 10-15ml
    - Levobupivacaine 0.125% and 0.0625%
  - Maintenance of analgesia
    - Infusion and PCEA: 0.0625% bupivacaine + fent 2.5microg/ml +/- clonidine
  - Intermittent bolus
    - Bupivacaine 0.125% or ropivacaine 0.2% + fent 2.5-5microg/ml (10-15ml)
    - 0.25% plain bupivacaine or ropivacine 0.2% (5-10ml)
    - 0.5% plain bupivacaine or ropivacaine (4-10ml)
    - 2% lignocaine + adrenaline 1:200 000 (4-10ml)
- ***Spinal***
  - Bupivacaine
  - Lignocaine and ropivacaine not licenced for intrathecal use
  - hyperbaric solutions:
    - e.g. heavy bupivacaine: 0.5% + 8% glucose
    - used to get higher block: 2.5-3ml should reach T6-10 in most non-pregant adults placed in recumbent position post injection
    - Complications: ↑risk hypotension
  - isobaric solutions:
    - produce lower block height
    - less hypotension

***Comparison of different LAs***

- Speed of onset = depends on local availability of unionised free base. Based on Fick's law of diffusion.
- Duration of action of LA = related to extent of PB at site of action + factors that affect removal of drug from the site (e.g. blood supply)

| | pKa | PB % | Max dose | Onset | Duration | Features | Intrathecal/ epidural |
|---|---|---|---|---|---|---|---|
| Lignocaine | 7.9 | 70 | 3mg/kg<br>7mg/kg | **Fast**<br>Low pKa → ↑molecules in unionised form → able to cross cell membrane rapidly | Medium:<br>60-90mins | Moderate vasodilation<br>Cerebral irritation before CC<br>Good sensory + motor block<br>Favourable recovery profile<br>Good for short spinal procedures | Epidural<br>Not for spinal due to risk of:<br>cauda equina syndrome +<br>transient radicular irritation/<br>transient neuro sx |
| Bupivacaine | 8.1 | 95 | 2mg/kg | Medium | Long | Good sensory; less motor block<br>Better for longer duration spinals/ long lasting post op analgesia<br>Prolonged cardiotoxicity in ↑doses | Both |
| Ropicavaine | 8.1 | 95 | 3mg/kg | Medium | Long | Less likely to prodice LA toxicity cf | Epidural |
| | | | | | | | |

| | | | | |
|---|---|---|---|---|
| | Slightly faster than bupivi | Slightly shorter than bupivi | bupivi | Not licenced for intrathecal use |

| Local anaesthetic | pKa | Onset | Protein binding (%) | Duration of action | Maximum dose (mg/kg) |
|---|---|---|---|---|---|
| Bupivacaine | 8.1 | Medium | 95 | Long | 2 |
| Levobupivacaine | 8.1 | Medium | 95 | Long | 2 |
| Ropivacaine | 8.1 | Medium | 94 | Long | 3 |
| Prilocaine | 7.7 | Fast | 55 | Medium | 6 (8 with adrenaline) |
| Lidocaine | 7.7 | Fast | 65 | Medium | 3 (7 with adrenaline) |
| Articaine | 7.8 | Very fast | 70 | Medium | 7 |
| Amethocaine | 8.5 | Slow | 75 | Long | 1.5 |
| Procaine | 8.9 | Slow | 6 | Short | 12 |
| Cocaine | 8.6 | | | Short | 1.5 |

## Describe how the baricity of the agents used and positioning of patients may affect the extent of block in spinal anaesthesia

***Background***

- LA = drugs that reversibly inhibit transmission of neural impulses in the applied region without affecting consciousness
- Spinal = LA +/- adjunct injected into subarachnoid space
  - LA act directly on SC; all modalities below upper limit of block affected
  - Blocks small, unmyelinated SY fibres then myelinated sensory + motor NB: SY block can exceed motor/sensory by 2 dermatomes
- Used for: lower abdo / perineal surg; LE; LSCS

***Patient position***

- **Seated:** saddle block → no higher than upper L levels → pelvic OT, spares ventilation
- **Supine:** LA pools ~T3 → lower abdo OT
- **contour of spinal canal**

***Baricity***

- Affects direction of spread
- Hyperbaric solutions: glucose → ↑gravity e.g. heavy bupivacaine (0.5% + 8% dextrose)
- Hypobaric solutions will rise against gravity
- Variability of spread ↑with isobaric

## Describe the drugs that may be injected into the intrathecal or epidural space as adjuvant agents to a central neuraxial block and discuss their risks and benefits

*See Regional and Local Anaesthetic section and Opioid section*

***Adjuvant agents to spinals and epidurals***

- **clonidine**
  - α2 adrenergic agonist
  - prolongs action of LA
  - activates –ve feedback mechanism → ↓catecholamine release → modulates input at the dorsal horn
  - also has cholinergic effects → ↑amount of ACh available centrally
  - adverse effect: hypotension, bradycardia, sedation
- **bicarbonate**
  - LA = weak bases in an acidic solution
  - Alkalinisation of LA → ↑non-ionised component → faster penetration of nerves
  - Literature controversial
- **opioids**
  - ↑duration of block
  - opioid Rs in dorsal horn + brainstem → binding causes hyperpolarisation of nerve membranes → ↓nerve transmission
  - substance P + glutamate release inhibited
  - synergistic effect
  - onset + duration of action depends on physicochemical properties
    - morphine: ↓lipid solubility → delayed onset + prolonged DoA
    - fentanyl: ↑lipid soluble cf morphine → faster onset; shorter DoA
- **Glucose**
  - Added to ↑baricity
  - E.g. heavy bupivacaine = dextrose 80mg/ml
  - Risk that glucose makes solutions hyperosmolar → ?neurotoxic

## Describe the physiological consequences of a central neuraxial block

*Physiological effect of spinal blockade at different levels*

| | Sensory | Motor | SY |
|---|---|---|---|
| Sacral S1-S5 | perineum, buttocks, skin over post legs, pelvic structures incl bladder + vagina | Loss of tone in anal + urethral sphincters<br>Anterior perineal muscles<br>Weakness in knee + ankle flexors | None – no sacral SY nerve fibres |
| Lumbar L1-5 | Anterior aspect of leg + groin | Hip flexors<br>Knee + ankle extensors | Little effect – SY chain rarely extends beyond L1 |
| Lower thoracic T10-12 | Skin of abdo at + below umbilicus<br>Lower intra-abdo organs | Lower abdo wall; lower intercostals → mild difficulty with deep inspiration | Vasodilation + loss of sweating in legs → ward, dry feet<br>Small ↓BP<br>Compensatory ↑HR |
| mid thoracic T6-9 | Upper abdo from lower border of ribcage to umbilicus<br>Upper intra-abdo organs + peritoneum | Lower intercostals → some difficulty deep breathing | GIT via coeliac plexus → arteriolar + venodilation of intestine → marked ↓SVR + ↑venous pooling → profound ↓BP with marked ↑HR |
| Upper thoracic T1-5 | Chest wall + medial arm<br>Thoracic structures | Upper thoracic intercostal → some difficulty deep breathing<br>Weakness arms + hands | Block SY outflow to heart (3-5th thoracic vertebral outflow) → -ve inotropic state with unopposed VA stimulation → CC + bradycardia<br>Vasodilation + ↓sweating in arms |
| Lower cervical C6-8 | Arms + hands | Shoulders, arms, hands | SY supply to stellate ganglion from C8 → blockade leads to ipsilateral Horners, partial ptosis, meiosis, anhydrosis, nasal stuffiness |
| Upper cervical C1-5 | Head + neck | Phrenic nerve → paralysis of diaphragm + apnoea | No SY outflow at this level |

## *Cardiovascular response to central neuraxial block*

***Overview***:

- central neuraxial blockade achieved by: subarachnoid (spinal) or epidural
- LA (bupivacaine, ropivavaine) +/- opioid (fentanyl, morphine)
- Effects are more pronounced in:
  - Elderly (↓physiological reserve)
  - Fixed cardiac output states
  - ↓blood volume

***CVS response***

- NB neuraxial block result in sympathectomy 2-6 dermatomes above the sensory block
- ↓ MAP due to:
  - blockade of α+ β SY chain fibres innervating venous smooth muscle + vasomotor tone
    - Run in thoracolumbar region (T5-T11) → level of block will affect degree of ↓MAP
    - MoA
      - Removes tonic SNS activity on vascular smooth muscle
      - Blocks α1 adrenoceptors (GPCR) → ↑PKC → ↑IP3/DAG → ↑Ca2+ → constriction
      - Blocks β2 receptors (GPCR) → ↑cAMP → ↓Ca2+ → dilation
    - Result
      - Vasodilation (arteriolar) → ↓afterload
      - Venodilation (**venous**) ↑capacitance → ↓VR → ↓preload → ↓CO
      - Veno effect >> arterial effect → 75% blood vol pools in venous circulation
- Bradycardia
  - Due to 3 mechanisms:
    - Bainbride reflex: stimulation of RA stretch Rs: ↓stretch → ↓VA afferent stimulation of medulla → ↑PSY activity → ↓HR
    - Direct effect on SA node by atrial stretching
    - Anaesthesia of T1-4 cardioaccelerator fibres
- Level of block of SNS + effect of CVS response
  - Sacral block: nil SY chain blockade (only PSY fibres) → minimal effect on peripheral vascular tone
  - mid thoracic/ renal level → ↓GFR → activation fo RAAS by ↓afferent arteriolar stretch
  - "high block": T1-T4 cardio-acceleratory centre → blockade → unable to ↑HR/contractility with SNS stimulation
  - brainstem block: inhibition of vasomotor centre → unable to activate SNS response → profound ↓MAP

***Detector/ compensatory systems***

- **high pressure baroreceptors (carotid sinus + aortic arch)**
  - sense: ↓stretch → ↓inhibitory input to SNS → stimulation of vasomotor centre
  - Result:
    - ↑SNS: ↑HR, ↑contractility; vasoconstriction; venoconstriction
    - activation of RAAS
      - ↑renin
      - ATII: direct vasoconstriction
      - ↑ADH
      - ↑H2O reabsorption from DVT
- **Low pressure baroreceptors (RA, great vessels)**
  - Sense: ↓stretch → ↓ANP secretion
  - Result: ↓inhibition RAA/ ADH system; ↓Na/H2O release

## *Describe the use of different sympathomimetics to treat hypotension occurring as a result of subarachnoid block. Outline advantages and disadvantages of these agents: PAST QUESTION*

- subarachnoid block = spinal block= intrathecal injection of LA agents in order to achieve anaesthesia
- Hypotension due to
  - Δtone of resistance vessels (↓SVR) + ↓VR to heart → ↓CO

| Sympathomimetic | Mechanism | Advantage | Disadvantage |
|---|---|---|---|
| Adrenaline | Direct α1+ß1 | Drug of choice for high spinal<br>Rapid onset<br>No tachyphylaxis | Arrhytmogenic<br>↑HR → ↑CMRO2 → may precipitate ischaemia<br>needs CVC |
| Ephedrine | ↑NAd release<br>↓NAd reuptake<br>inhibit MAO<br>indirect α1 + ß1 | Drug of choice for obstetric (doesn't affect uterine BF)<br>Compatible with PIVC access<br>Longer DoA<br>Not metabolised by MAO/ COMT | Tachyphylaxis<br>Foetal acidosis<br>Arrhythmogenic<br>Renal excretion |
| Noradrenaline | Direct α1 | | Reflex ↓HR→ not appropriate for high spinal<br>↑CMRO2<br>extravasation → tissue necrosis |
| Phenylephrne | Direct α1 | | Asabove |
| Metaraminol | Direct α1<br>Indirect α1 | PIVC | Reflex ↓HR→ not appropriate for high spinal<br>Tolerance from NAd exhaust at synapse |
| Isoprenaline | Direct ß1 | | Vasodilating (via ß2) |
| Dobutamine | Direct ß1 | | Minimal vasoconstriction → thereforenot usedin rx subaachnoi hypotension |
| Dopamine | ß1 low dose<br>α1 high dose | Less arrhythmogenic vs. adrenaline | Difficult to titrate between dose effects<br>More arrhythmogenic vs. NAd |
| Vasopressin | V1 | Non-adrenoceptor pathways → useful in pts who are B blocked | vasoconstrictor → peripheral + splanchnic ischamia<br>Reflex ↓HR→ not for high pinal<br>Coronary artery vasoconstriction → can precipitate ischaemia |

- common features of agents
  - pharmaceutical presentation: all require dilution before use
  - agents with strong vasoconstricting effect have risk of tissue necrosis if extrvasation occurs
  - risk of HTN
  - can cause tachycardia via direct effects or reflex bradycardia
- Relevant patient problems that contribut to advantages/ disadvantages:
  - Age/ intercurrent illness esp. cardiovascular disease + antihypertensive meds
  - Pregnancy + childbirth
  - Drug interactions i.e. MAOI

## *Complications of central neuraxial anaesthesia: MAKEUP*

***Common immediate:***

- failure/ incomplete block
- hypotension
- N+V 2o hypotension
- Shivering/ itching
- Temporary backache

***Uncommon immediate***

- bradycardia 2o block of SY supply to heart
- impairment of accessory muscles of respiration
- horners syndrome if stellate ganglion involved
- phrenic nerve paralysis if C3-5 roots involved
- CN palsies

***Uncommon late***

- dural tap headache
- urinary retention
- neurological damage 2o direct trauma/ epidural haematoma/ spinal cord ischaemia
- epidural abscess / meningitis / arachnoiditis
- Permanent injury 1:25 000-1:50 000

**High spinal / complete spinal block**

- large vol of LA inadvertently injected intrathecally at lumbar level but then rapidly spreads cranially
- Mechanism
  - Unknown
  - Consider:
    - Drug factors: block height more dependent on dose than vol; baricity; prior drug administration
    - Patient factors: body morphology (↑BMI → ↑intraabdo pressure → ↓thecal vol), anatomical / pathological factors

        - Technique factors: higher lumbar insertion; position at and following injection; spinal needle (finer gauge + cephalad direction ↑risk)
- Clinical symptoms
    - Cardioresp: hypotension, bradycardia, resp compromise, apnoea, ↓sats, cardiac arrest (asystole)
    - Neuro: nausea, anxiety, arm/hand paralysis, high sensory level block, CN involvement, LOC
- Progression of symptoms/ signs
    - rapid onset analgesia in lower limbs + pelvis; minor ↓BP 2o arteriolar + enous dilation in legs → compensatory ↑HR
    - <30s → block spreads up to lower thoracic region → minor difficulty breathing + loss of sensation over abdo
    - mid thoracic level reached → coeliac plexus bocked → loss of SY tone to GIT → arteriol + venous dilation → severe hypotension with marked compensatory tachycardia
    - as block spreads to upper thoracic region → ↑SOB
    - when block reaches SY outflow to heart at T3-5 roots → loss of +ve chronotrope + inotrope effects → unopposed VA stimulation results in bradycardia or asystole and CC
    - block to lower cervical region → weakness in arms and hands, shoulders, head + horners + phrenic nerve paralysed → apnoeic
    - NB CC before resp failure
- Management
    - Bradycardia: vagolytics e.g. atropine; sympathomimetics e.g. adrenaline, ephedrine
    - Hypotension: vasopressors e.g. metaraminol, phenylephrine, fluid, leg elevation
    - Resp dysfunction: oxygenation, I+V
    - LOC: secure airway, supportive measures

*The poorly functioning epidural: MAKEUP*

| Pattern of failure | Remedy |
|---|---|
| **Global failure** | |
| - no detectabl block despite at least 10ml 0.25% bupivacaine or equivalent | Resite epidural |
| **Partial failure** | |
| Unilateral block<br>- feel both feet to assess whether they are symmetrically warm + dry<br>- See if pattern matches the distribution of pain | - Top up epidural with painful side in dependent position<br>- Use LA + 50-100microg fent<br>- Withdraw catheter 2-3cm and give further top up<br>- Resite epidural |
| Missed segment<br>- true missed segments are rate<br>- commonly missed segment felt in the groin is a partial unilateral block | - top up with opioid e.g. 50-100microg fent → intrathecal MoA will ↓segmental effects<br>- continue as per unilateral block |
| Back pain<br>- severe back pain = associated with occipito-posterior position of foetus and may require dense block to establish analgesia | - top up with more LA and opioid |
| Perineal pain | - check sacral block and that bladder is empty<br>- top up with more LA in sitting position<br>- continue as per unilateral block |

## Describe the anatomy of the vertebral column spinal cord and meninges relevant to the performance of central neuraxial block with appropriate surface markings.

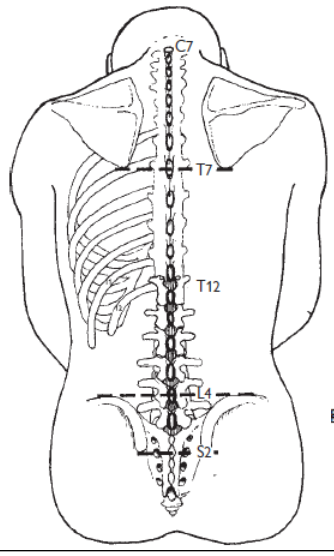
**Spinal and epidural anatomy**

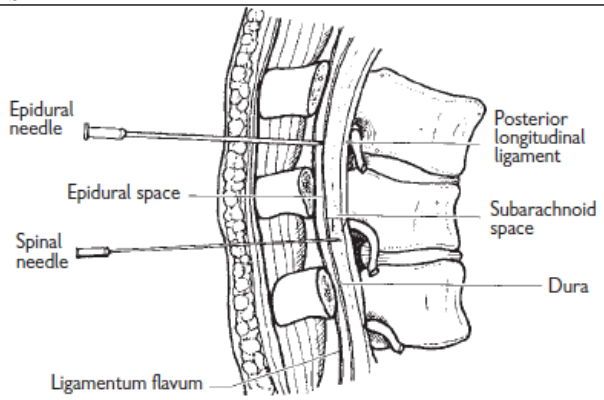
***Anatomical landmarks***

- C7: bony knob at base of neck
- T7-8: lower limits of scapulae
- L2: terminal point of 12th ribs
- L4: line across iliac crests (Tuffiers line)
- S2: posterior iliac spines

***Internal anatomy***

- Thoracic area: SP point down; interlaminar space few mm's
- lumbar region: SP nearly perpendicular to VB
- Spinal cord terminates at L1 in adults and L3 in infants
- Subarachnoid space
    - ends at S2 in adults; lower in children
    - extends laterally along the nerve roots to the dorsal root ganglia
    - continuous with intracranial → excessive migration can → blockade of CNs
- Epidural (extradural) space
    - lies between the walls of the vertebral canal + spinal dura mater
    - potential low pressure space
    - communicates with paravertebral spaces via foraminae
    - occupied by areolar tissue, loose fat, internal vertebral venous plexus




g. 41.26 Subarachnoid and epidural spaces.

## Describe the dermatomal + myotome innervations

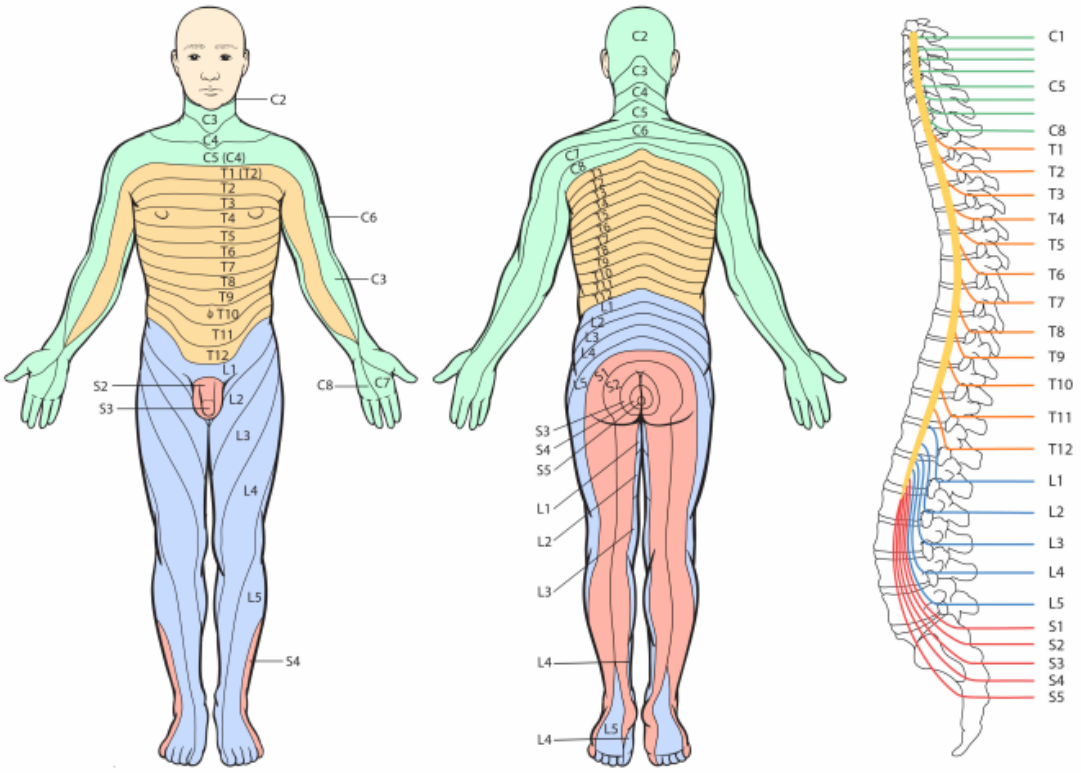



**Table 3. Cervical And Lumbosacral Dermatomes And Myotomes.**

| Spinal level | Key sensory area for dermatomal testing | Myotome |
|---|---|---|
| C5 | Radial antecubital fossa | Elbow flexors (biceps*, brachialis, and brachioradialis*) |
| C6 | Thumb | Wrist extensors (extensor carpi radialis longus and brevis) |
| C7 | Middle finger | Elbow extensors (triceps*) |
| C8 | Little finger | Finger flexors* (distal phalanx—flexor digitorum profundus) |
| T1 | Ulnar antecubital fossa | Hand intrinsics (interossei) |
| L2 | Mid-anterior thigh | Hip flexors (iliopsoas) |
| L3 | Medial femoral condyle | Knee extensors* (quadriceps) |
| L4 | Medial malleolus | Ankle dorsiflexors (tibialis anterior) |
| L5 | Dorsal second/third toe web space | Long toe extensors (extensor hallucis longus) |
| S1 | Lateral heel | Ankle plantar flexors* (gastrocnemius, soleus) |

* Commonly tested reflexes

## Describe the midline and paramedian approaches to the sub-arachnoid space and epidural space

**Epidural**

***Prerequesites***

- Informed consent: complications most relevant include: failure, LA toxicity, nerve damage
- Absence of contraindications
- Baseline temperature, HR, BP: i.e. afebrile, HR <90, BP>100/60
- Monitoring
- Patent wide bore IV cannula (at least 18G) with fluid administration set attached
- Resus/ intubation equipment available
- O2 therapy available
- Naloxone, vasopressor available
- Assistance
- Environment: well lit, quiet, calm

***Cannulation techniques***

- Patient position
  - Lateral position: optimal flexion of spine + widening of distance between spinous processes → but NB commonly distors midline anatomy
  - Sitting position ↑hydrostatic pressure in CSF + may ↑risk of inadvertent dural puncture
- Midline technique
  - Easiest approach + passes through less sensitive structures
  - Identify interspace → tuohy needle introduced → directed slightly cephalad in the midline between 2 spinous processes at level of desired block
  - Needle passes through: supraspinous ligament → interspinous ligament → ligamentum flavae → enters epidural space
  - A click or pop is felt; ~4-6cm depth
- Paramedian technique
  - Better suited to narrow interspaces or difficulty with flexion
  - Tuohy needle introduced ~1-2cm lateral to mid point of SP immediately below level of desired block
  - Needle advanced perpendicular to skin to contact vertebral lamina → withdrawn slightly, redirected 15o medially + 30i cephalad to pass over lamina through interlaminar space → pop through ligamentum flavum → enters epidural space
- For both techniques the identification of end point = loss of resistance
- Spinal blocks should be carried out caudal to L3/4 to avoid trauma to tail end of spinal cord (conus)

***Anaesthetic***

- LA can be administered by bolus or continuous infusion through indwelling catheter for longer DoA
- Intensity of epidural block = determined by concentration + type of LA solution used
  - Opioids administered with LA solution augment sensory blockade, but spare motor blockade → analgesia
  - Epinephrine + clonidine have been used to prolong the block
- Spread of LA = related to vol injected → occurs in cranial + caudal directions
  - Highest + lowest level of the block can be modified by:
    - changing level of cannulation
    - appropriate positioning of patient (spread is influenced by gravity

***Post op monitoring***

- height + spread monitored: testing for motor block + loss of sensation to cold or light touch
- BP: rx fluids + vasopressors
- HR: bradycardia can occur due to unopposed VA cardiac stimulation if SY outflow to heart (T3,4,5) is blocked → rx: anticholinergic agent
- RR: depression of respiration can be 2o phrenic nerve outflow blocked (C3,4,5) → resp support
- Complications
  - Common:
    - Incomplete blockade/ failure of blockade
    - Hypotension → N+V
    - Localised bruising at site of injection resulting in short term backache
    - Dural tap headache
    - Pruritis if opioids used
  - Uncommon
    - Neurological damage due to direct trauma or epidural haematoma formation → opstruction of venous drainage → spinal cord ischaemia
    - Unplanned high block → CN lesions
    - Horners syndrome
    - Total spinal blockade