REGIONAL AND LOCAL ANAESTHESIA

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Regional and Local Anaesthesia

Annelise Kerr

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
   - RMP = -70mV in nerve; -90mV in skeletal muscle cells

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
   - Sodium/potassium ATPase: 3Na+ out for 2K+ in. Consequences:
     - Osmotic effect: ECF [Na+] balances osmotic effect of ICP [K+]
     - 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
   - Nerst applied:
     - RMP has ↑K permeability ⇒ net efflux of +vely charged K down conc gradient ⇒ drives membrane potential towards Nerst potential for K+
     - RMP ↓permeability to Na+ ions
   - Therefore: measured neuronal RMP (-70mM) = close to Nerst potential for K+

2. **Goldman–Hodgkin-Katz equation**
   - Considers all ionic permeabilities and concentrations ⇒ RMP more precisely quantified

3. **Gibbs Donnan effect**

Typical RMPs of various cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>RMP (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelinated Aseae</td>
<td>-70</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>-90</td>
</tr>
<tr>
<td>Cardiac myocyte</td>
<td>-60</td>
</tr>
<tr>
<td>Cardiac pacemaker</td>
<td>fixed RMP (prepotential -60)</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>fixed RMP (-20 to -60)</td>
</tr>
</tbody>
</table>

**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
    - Nerst
    - 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
Conduction of nerve impulses: Salutatory conduction

- Electrical depolarisation 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 CM

- Velocity of conduction is dependent on several factors:
  - Axon diameter: 1 diameter → 1 resistance to flow → 1 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+ 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
    - Salutatory 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 into 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

- Salutatory conduction: propagation of AP along myelinated axons, whereby wave of depolarisation “jumps” from one rode of Ranvier to the next
REGIONAL AND LOCAL ANAESTHESIA

Annelise Kerr

- 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
    - 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

Write notes on the axonal membrane: PAST QUESTION

Axon
- fibre like structure that leaves the cell body
- contains mitochondria, 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 depolarisation 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
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  - 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
    - Postsynaptic 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
2. **Summation of EPSP not reaching threshold**
   - EPSP: partial depolarization in postsynaptic neuron → excitability
   - Post synaptic membrane only depolarizes 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 → TCl 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-synaptic potential (EPSP) → not enough to reach threshold
5. Multiple EPSPs temporally + spatially summate to achieve threshold potential in post-synaptic membrane → propagation of signal

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**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 Fick’s law of diffusion
  \[
  \text{Rate of diffusion} = \frac{\text{area}}{\text{thickness}} \times \frac{\text{sol}}{\text{MW}} \times \text{concentration gradient}
  \]
- 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

**Nature of blockade / differential nerve block**
- \( Cm = \text{minimal conc of lignocaine required to achieve blockade} \)
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 temporary blockade of neuronal transmission by blocking the voltage-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 1pH
    - 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 + A delta > A y > A alpha
  - I.e: pain > cold + warmth > touch > deep pressure > motor function

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

<table>
<thead>
<tr>
<th>Esters</th>
<th>Amides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ester linkage (R-CO-O-R1)</td>
<td>Amide linkage (R-NH-CO-R1)</td>
</tr>
<tr>
<td>E.g. procaine, amethocaine, cocaine</td>
<td>E.g. lignocaine, bupivacaine, ropivacaine, dibucaine, prilocaine</td>
</tr>
</tbody>
</table>

Structure activity relationships of LAs

- Hydrophilic portion (usually tertiary amine): determines degree of ionisation
- Lipophilic portion (usually aromatic ring): ↑ lipid solubility → ↑ 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
- Isomerism
  - Bupivacaine: racemix mix of S and R enantiomer
  - Levobupivacaine: S-enantiomer of bupivacaine; ↓ toxic
  - Ropivacaine: pure S-enantiomer; R-enantiomer ↓ potent + ↑ toxic
Factors affecting the speed of onset and duration of effect of local anaesthetics when used to produce peripheral nerve block:

**PAST QUESTION**

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

**Background**
- LA = drug that inhibit transmission of nerve impulses in applied region without affecting level of consciousness
- MoA:
  - LAs diffuse across phospholipid bilayer of the nerve fibre \(\rightarrow\) enter axoplasm
  - Protonated + ionised \(\rightarrow\) binds internal surface of voltage gated Na channels (while in activated open state)
  - Maintains the inactivated closed state \(\rightarrow\) inhibit nerve impulse propagation
- Other minor MoA:
  - LAs bind to external opening of Na channel to facilitate above mechanism
  - LAs dissolve in phospholipid bilayer \(\rightarrow\) expansion \(\rightarrow\) 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:**
  - \[\text{Rate of diffusion} = \frac{\text{area}}{\text{thickness}} \times \frac{\text{sol}}{\sqrt{\text{MW}}} \times \text{conc gradient} \]
- **Drug factors**
  - pKa (1o factor)
    - Ionised drugs = poorly lipid soluble \(\rightarrow\) onset of action
    - LAs = weak base: \(\downarrow\)pKa = \(\downarrow\)absorption into nerve tissues; \(\uparrow\)pKa = \(\uparrow\)effective within nerves
    - \(\downarrow\)pKa \(\rightarrow\) \(\uparrow\)ionised fraction
  - MW; \(\downarrow\)MW \(\rightarrow\) \(\uparrow\)diffusion \(\rightarrow\) faster onset (NB all have similar MW therefore little impact on diffusion)
  - Lipid solubility and effect on potency + PB: \(\uparrow\)lipid solubility \(\rightarrow\) \(\uparrow\)diffusion \(\rightarrow\) faster onset
  - Concentration gradient + vol added
    - \(\uparrow\)dose \(\rightarrow\) \(\uparrow\)concentration gradient \(\rightarrow\) \(\uparrow\)diffusion \(\rightarrow\) faster onset
    - \(\uparrow\)vol \(\rightarrow\) area of contact with target nerve \(\rightarrow\) \(\uparrow\)diffusion \(\rightarrow\) faster onset
  - Diffusion distance
  - Area of diffusion
  - Alkalisation: adding NaHCO3 \(\rightarrow\) \(\uparrow\)ionised fraction \(\rightarrow\) \(\uparrow\)onset of action
- **Patient factors**
  - Site of administration
    - \(\downarrow\)diffusion distance \(\rightarrow\) \(\uparrow\)diffusion \(\rightarrow\) faster onset. Depends on location of injection + proximity to target nerve
  - Nerve structure + function
    - \(\uparrow\)nerve diameter \(\rightarrow\) \(\uparrow\)diffusion distance \(\rightarrow\) slower onset
    - \(\uparrow\)nerve firing rate \(\rightarrow\) \(\uparrow\)onset of action (frequency dependent blockade)
    - myelinated fibres blocked faster than unmyelinated fibres (continuous conduction)
    - order of onset: \(\beta\) > Adelta > A > C (slowest); autonomic >pain/sensory > motor
  - \(\downarrow\)1-acid glycoprotein \(\rightarrow\) unbound LA \(\rightarrow\) faster onset
  - Tissue pH + electrolyte disturbances
    - acidosis \(\rightarrow\) ionised fraction \(\rightarrow\) \(\downarrow\)lipid solubility \(\rightarrow\) slower onset (i.e. infected tissue \(\rightarrow\) slower onset)
    - hyperkalaemia \(\rightarrow\) membrane depolarisation \(\rightarrow\) more Na+ channels in active state \(\rightarrow\) potentiates LAs \(\rightarrow\) faster onset
  - Pregnancy

**Factors that affect DURATION OF ACTION**
- **Drug factors**
  - Protein binding (1o factor)
    - \(\uparrow\)PB \(\rightarrow\) longer binding to neuronal membrane proteins \(\rightarrow\) \(\uparrow\)DoA
    - e.g. lignocaine 70% vs. bupivacaine 95%
  - Intrinsic vasodilator activity
    - \(\uparrow\)vasodilatation \(\rightarrow\) \(\uparrow\)systemic absorption \(\rightarrow\) \(\downarrow\)DoA
    - vasodilators: prilocaine > lignocaine > bupivacaine > ropivacaine
    - vasoconstrictors: cocaine
  - Lipid solubility
    - \(\uparrow\)lipid solubility \(\rightarrow\) \(\uparrow\)potency; \(\uparrow\)sequestration into lipid rich compartments (\(\downarrow\)drug available for metabolism); \(\uparrow\)PB \(\rightarrow\) \(\downarrow\)free fraction
  - Additives
    - Adrenaline: vasoconstriction
    - Clonidine: \(\uparrow\)DoA spinal, epidural, peripheral nerve blocks
    - Opioids: \(\uparrow\)DoA spinal + epidural
- **Dose**
  - \(\downarrow\)pKa \(\rightarrow\) \(\uparrow\)ionised fraction \(\rightarrow\) \(\uparrow\)ion trapping within axoplasm \(\rightarrow\) \(\downarrow\)duration
- **Patient factors**
  - Site of administration:
    - \(\uparrow\)regional blood flow \(\rightarrow\) \(\uparrow\)systemic absorption, \(\downarrow\)DoA
    - Systemic absorption in order of \(\downarrow\)rate: intercostal > caudal > epidural > peripheral nerve > subcut infiltration
  - Metabolism
    - \(\text{faster metabolism} \rightarrow\) \(\downarrow\)duration of action. In general esters have shorter DoA than amides
    - active metabolites \(\rightarrow\) \(\downarrow\)duration of action e.g. ropivacaine \(\rightarrow\) 3-hydroxyropivacaine (active)
Potency of local anaesthetics: MAKEUP

<table>
<thead>
<tr>
<th>Minimum effective concentration of LA (Cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- minimum concentration of a LA that results in complete block of a nerve fibre in 50% of subjects under standard conditions</td>
</tr>
<tr>
<td>- measure of potency: ( \uparrow \text{potency} \rightarrow \downarrow \text{Cm} )</td>
</tr>
<tr>
<td>- factors that affect Cm:</td>
</tr>
<tr>
<td>- lipid solubility: ( \uparrow \text{lipid solubility} \rightarrow \downarrow \text{Cm} )</td>
</tr>
<tr>
<td>- nerve fibre diameter: ( \uparrow \text{diameter} \rightarrow \uparrow \text{Cm} )</td>
</tr>
<tr>
<td>- tissue pH: ( \uparrow \text{pH} \rightarrow \downarrow \text{Cm} )</td>
</tr>
<tr>
<td>- frequency of nerve stimulation: ( \uparrow \text{frequency} \rightarrow \downarrow \text{Cm} )</td>
</tr>
<tr>
<td>- pregnancy: ( \uparrow \text{sensitivity} ) may be present</td>
</tr>
</tbody>
</table>

Factors affecting potency of LAs

- lipid solubility (1st factor)
  - determines potency
  - \( \uparrow \text{lipid solubility} \rightarrow \downarrow \text{potency} \) = minimum amount of drug required to produce given effect
  - \( \uparrow \text{potency} \rightarrow \downarrow \text{Cm} \) = molecules able to penetrate the nerves \( \rightarrow \) less drug required to give same blockade

- intrinsic vasodilatory activity
  - all are vasodilators except cocaine, ropivacaine, and levobupivacaine = vasoconstrictors
  - \( \uparrow \text{vasodilation} \rightarrow \downarrow \text{systemic absorption} \)

- Additives
- Tissue pH
- Tissue distribution

Pharmacodynamics

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

NB

- pKa
  - \( \text{pKa} \) of a chemical compound represents the pH at which its ionised and non-ionised forms are in equilibrium
  - \( \text{pKa} \) 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 \( \rightarrow \) soluble in water \( \rightarrow \) suitable for injection
  - At physiological pH, proportion of drug that dissociates into free base (which is lipid soluble) is determined by its \( \text{pKa} \rightarrow \) non-ionised portion passes through lipid cell membrane to inner axon where re-ionisation occurs \( \rightarrow \) re-ionised portion of LA blocks Na channels
  - Closer the \( \text{pKa} \) of the drug is to physiological pH (7.4) \( \rightarrow \) the \( \uparrow \text{free base (non-ionised drug) present} \rightarrow \) faster block
  - than hupivacaine. Ropivacaine has \( \uparrow \text{lipid solubility} \rightarrow \uparrow \text{affinity} \rightarrow \) penetration of myelin sheath \( \rightarrow \) 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 vasodilatory activity
- Vasoconstrictor
- Site of administration: different regional blood flow; intercostal > caudal > epidural > brachial plexus > spinal > SC
- Rate of \( \uparrow \text{[plasma]} \)

Factors that affect distribution

- PB
  - \( \text{Parallels lipid solubility} \)
  - \( \text{Amides} > \text{esters} \)
  - \( \text{Bupivacaine} > \text{ropivacaine} > \text{lignocaine} > \text{prilocaine} \)
  - \( \alpha_1\text{-acid glycoprotein: } \uparrow \text{affinity} \)
  - \( \text{albumin: } \uparrow \text{capacity} \)
- Regional blood flow
- Placental transfer: \( \uparrow \text{PB} \rightarrow \downarrow \text{transfer; ion trapping} \)
- Lung extraction from circulation

Metabolism + elimination

- esters
  - \( \text{Rapidly hydrolysed by plasma cholinesterases + other esterases } \rightarrow \text{inactive metabolites; NB PABA } \rightarrow \text{hypersensitivity reactions} \)
  - \( \downarrow \text{metabolism} \rightarrow \uparrow \text{risk systemic toxicity} \)
  - \( \text{cocaine: hepatic hydrolysis; inactive metabolites; renal excretion} \)
- Amides
  - \( \text{Hepatic N-de-alkylation + hydroxylation} \)
  - \( \text{Slower metabolism } \rightarrow \downarrow \text{accumulation } \rightarrow \uparrow \text{risk toxicity} \)
  - \( \downarrow \text{metabolism} \rightarrow \downarrow \text{risk systemic toxicity} \)
  - \( \text{minimal renal excretion of unchanged drug} \)
### Amides

<table>
<thead>
<tr>
<th>Chem</th>
<th>Lignocaine</th>
<th>Bupivacaine</th>
<th>Ropivacaine</th>
<th>Prilocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amide</strong></td>
<td>Tertiary amine; lipophilic aromatic ring, amide linkage, hydrophilic tertiary amine</td>
<td><strong>Pipecoloxylide</strong> → chiral centre</td>
<td><strong>Pipecoloxylide</strong> → chiral centre</td>
<td>Amide derivative of toluidine</td>
</tr>
<tr>
<td><strong>Achiral</strong></td>
<td>pH 6.4</td>
<td>Butyl side chain → ↑ lipid solubility + PPB</td>
<td>Propyl side chain (cf bupivacaine - bupyl) → ↑ lipid solubility</td>
<td>MW 234</td>
</tr>
<tr>
<td><strong>MW</strong></td>
<td>234</td>
<td>288</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td><strong>Isomer</strong></td>
<td>Racemic mix S+R enantiomers</td>
<td>Pure S-enantiomer</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>O/W PC</strong></td>
<td>2.9</td>
<td>Hexanol:buffer coefficient = 28</td>
<td>Hexanol:buffer coefficient = 2.9</td>
<td></td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>More potent than ropivacaine</td>
<td>Slightly less potent than bupivacaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vasodilator?</strong></td>
<td>Yes – mild</td>
<td>No – vasoconstrictor properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>Fast acting, short duration LA: topical/ regional/ neuraxial</td>
<td>Slow acting, long duration amide LA</td>
<td>Slow acting, long duration amide LA</td>
<td>Fast acting, short duration amide LA for IV or as compound for EMLA</td>
</tr>
<tr>
<td><strong>Pres</strong></td>
<td>CCS 0.5-2% lignocaine hydrochloride (+/- 1:200 000 adrenaline) (4 solubility overcome by hydrochloride → buffered to pH 6) Gél/ointment/spray Long shelf life</td>
<td>CCS racemic bupivacaine (S + R enantiomers) 0.25-0.5% (+/- 1:200 000 adrenaline) heavy solution: 0.5% + 80mg/ml glucose 0.1% + 2microg/ml fentanyl</td>
<td>CCS racemic ropivacaine hydrochloride monohydrate (S + R enantiomers) 0.2/0.75/10mg/ml ropivacaine hydrochloride</td>
<td>CCS 0.5/1/2/4% prilocaine hydrochloride + 3% with 0.03IU felypressin/ml Also in EMLA 5%:1:1 oil in water emulsion</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>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 → disrupts further neural transmission</td>
<td>Cardiotoxic – binds to myocardial proteins → blocks cardiac Na channels + 4 rate of ↑ of phase 0 of cardiac AP</td>
<td>Less cardiotoxic than bupivacaine: in toxic conc → 4PVR 4 myocardial contractility → ↓BP biphasic vascular effect: vasoconstriction at 4cone</td>
<td>Mild ↑SVR and MAP at low doses</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>reversible neural blockade</td>
<td>blockade of inactivated Na channels - ↓ phase IV/ cardiac AP depolarisation - ↓AP duration - ↓ Refractory perior - ↓conduction velocity</td>
<td>less cardiotoxic than bupivacaine: in toxic conc → 4PVR 4 myocardial contractility → ↓BP biphasic vascular effect: vasoconstriction at 4cone</td>
<td>Mild ↑TSR and MAP at low doses</td>
</tr>
<tr>
<td><strong>CVS</strong></td>
<td>Bronchodilation</td>
<td></td>
<td>less cardiotoxic than bupivacaine: in toxic conc → 4PVR 4 myocardial contractility → ↓BP biphasic vascular effect: vasoconstriction at 4cone</td>
<td></td>
</tr>
<tr>
<td><strong>Resp</strong></td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxicity/SE</strong></td>
<td>CVS: 4PVR, 4myocardial contractility → hypotension + possible cardiovasc collapse</td>
<td>CNS: dose dependent excitatory effects (circumoral tingling, paraesthesia, twitching, confusion, seizure, 4LOC, coma</td>
<td>Methaemoglobinaemia at doses &gt;600mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RS: resp depression</td>
<td>CVS: 4PVR 4 myocardial contractility → hypotension + cardiac collapse; affects K and Ca2+ channels</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doses &gt;600mg: methaemoglobinaemia due to metabolite O-toluadine</td>
<td>NB bupivacaine more cardiotoxic → binds to cardiac Na+ channels + dissociates less easily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CNS:</strong></td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>CVS:</strong></td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Route/dose</strong></td>
<td>Topical/ infiltration/ intrathecal/ epidural</td>
<td>Topical/ infiltration/ intrathecal/ epidural</td>
<td>Not for spinal/ IV</td>
<td>Max safe dose 6mg/kg or 8mg/kg with adrenaline</td>
</tr>
<tr>
<td></td>
<td>Max safe dose 3mg/kg (7mg/kg with adrenaline) Arthralgia: 1mg/kg over 2 mins → infusion</td>
<td>Max safe dose 2mg/kg (+/- adrenaline)</td>
<td>Topical/ epidural/ infiltration</td>
<td>Max safe dose 3mg/kg (+/- adrenaline)</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>3min</td>
<td>&lt;10-20mins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### LAN and RLA

Annelise Kerr
REGIONAL AND LOCAL ANAESTHESIA

Annelise Kerr

Duration  60-120min  5-15hours

A  4
l lipid solubility, N-heptane buffer = 3  1
l lipid solubility, N-heptane/buffer 27  1
l lipid solubility, N-heptane/buffer = 9  1
l lipid solubility, N-heptane/buffer = 1

pKa  7.9 (weak base)  8.1 (weak base)  7.9 (weak base)

%IU  25%  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%

M  Liver  N-dealkylation with hydrolysis to monoethanolamine (MEGX) + xylidide
Active metabolites (10% activity)

E  Urinary (<10% unchanged)
Clearance 10ml/kg/min

T1/2  90-120min  30min  2hr

Special points
Metabolites may ↓ seizure threshold
4-clearance in cardiac + hepatic failure

Ideal epidural: ↓ lipid solubility  penetration thick motor fibres
(↓tendency to block A-delta and C fibres  motor anaesthesia
4-intense/duration – good for obstetrics and post op pain)

Esters

<table>
<thead>
<tr>
<th>Chem</th>
<th>Procaine</th>
<th>Cocaine</th>
<th>Tetracaine (Amethocaine )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st synthetic injectable LA of ester class</td>
<td>Ester of benzoic acid</td>
<td>Potent ester</td>
<td></td>
</tr>
<tr>
<td>Uses</td>
<td>LA, use now confined to infiltration anaesthesia</td>
<td>Topical vasoconstrictor (ENT/ nasal fibreoptic intubation)</td>
<td>Ophthalmology LA to eye</td>
</tr>
<tr>
<td>Pres</td>
<td>CCS 0.25/0.5-5%</td>
<td>Topical solution/ pastes 1-4% + moffats 2ml 8% + 2ml 1% sod bic + 1ml 1:1000 adrenaline</td>
<td>CCS amethocaine hydrochloride 0.5/1%</td>
</tr>
<tr>
<td>Action</td>
<td>As per amides</td>
<td>Blocks uptake of NAd and dopamine  vasoconstriction + CNS excitation</td>
<td>Also LA properties as per amides</td>
</tr>
<tr>
<td>CNS</td>
<td>Low potency</td>
<td>Hyperreflexia, mydriasis, ↑IOP</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>Dose dependent:  - low: ↓HR due to ↑VA tone  - moderate: ↑BP, ↑HR (CNS stimulation + block NAd reuptake peripherally  intense peripheral vasoconstriction)  - large: myocardial depression; may precipitate VF and CC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resp</td>
<td>Stimulates resp centre + ↑ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>Hyperdynamic bowel sounds, N+V, ↑body temp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Toxicity/SE
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 hyпоxemia (4-uterine blood flow)
Rx toxicity: GTN, IV BZDs ?esmolol
Local irritation/ burning/ stinging on instillation
Blurred vision, keratitis uncommon

Route/dose
Max safe dose 8mg/kg

Onset
Slow  Fast 15-30min  Very fast 10-20s

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

10
Compare the pharmacology of ropivacaine and bupivacaine, and explain why ropivacaine may be considered a safer agent than bupivacaine: PAST QUESTION

<table>
<thead>
<tr>
<th>Property</th>
<th>Mechanism</th>
<th>Ropivacaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isomers</td>
<td>Pure S enantiomer</td>
<td>Racemix 1:1 mixture of R and S enantiomers</td>
<td></td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>$\downarrow$lipid solubility $\rightarrow$uptake by CNS/CVS $\rightarrow$.$\downarrow$toxicity</td>
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<td>Vasoactivity</td>
<td>$\uparrow$Local vasodilation $\rightarrow$.$\uparrow$toxicity</td>
<td>$\uparrow$vasoconstriction at low doses</td>
<td>$\uparrow$vasodilation at low doses (used with Ad) $\Rightarrow$.$\uparrow$systemic absorption</td>
</tr>
<tr>
<td>Clearanee</td>
<td>$\uparrow$systemic clearance $\Rightarrow$.$\downarrow$toxicity</td>
<td>Clearance 0.8L/min hepatic</td>
<td>Clearance 0.5L/min hepatic</td>
</tr>
<tr>
<td>Cardiac receptor action</td>
<td>$\uparrow$affinity cardiac Na$^+$ channels $\rightarrow$.$\uparrow$cardiotoxicity</td>
<td>Faster dissociation from cardiac Na channels $\rightarrow$.$\downarrow$toxicity</td>
<td>Slower dissociation from cardiac Na$^+$ channels $\rightarrow$.$\uparrow$toxicity</td>
</tr>
</tbody>
</table>

**Ropivacaine**

- Shorter propyl side chain, lower O:W 2.9 $\Rightarrow$.$\downarrow$solubility
- Lower butyl side chain, higher O:W 28 $\Rightarrow$.$\uparrow$solubility

**Bupivacaine**

- Longer butyl side chain, higher O:W 28 $\Rightarrow$.$\uparrow$solubility
- Longer half-life 160mins

For comparison see above

### Reasons for safety of ropivacaine

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**Ropivacaine**

- $\downarrow$toxicity
- $\downarrow$systemic absorption

**Bupivacaine**

- $\downarrow$systemic absorption
- $\downarrow$toxicity

<table>
<thead>
<tr>
<th>Lipid solubility</th>
<th>R enantiomer $\Rightarrow$lipid solubility $\Rightarrow$uptake by CNS/CVS $\Rightarrow$.$\downarrow$toxicity</th>
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</tr>
</tbody>
</table>

**Ropivacaine**

- $\downarrow$toxicity
- $\downarrow$systemic absorption

**Bupivacaine**

- $\downarrow$systemic absorption
- $\downarrow$toxicity
Write brief notes on the physicochemical properties of lignocaine: PAST QUESTION

<table>
<thead>
<tr>
<th>Physicochemical property</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Amide LA; Weak base</td>
</tr>
<tr>
<td>MW</td>
<td>234</td>
</tr>
<tr>
<td>pKa</td>
<td>7.9</td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>Hexanol-buffer coeff = 3</td>
</tr>
<tr>
<td>Protein binding</td>
<td>70% plasma protein bound (1o α1 acid glycoprotein)</td>
</tr>
<tr>
<td>Intrinsic vasodilator activity</td>
<td>Low dose → vasodilate, high dose → vasoconstrict</td>
</tr>
<tr>
<td>Isomerism</td>
<td>Racemix mixture 1:1 R and S enantiomers</td>
</tr>
<tr>
<td>Stable/ long shelf life</td>
<td>Yes – poorly water soluble so formulated as hydrochloride salt</td>
</tr>
</tbody>
</table>

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 piperaciloxylidide 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

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<tr>
<td>Structure</td>
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</tr>
<tr>
<td>MW</td>
<td>288</td>
</tr>
<tr>
<td>pKa</td>
<td>8.1</td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>Hexanol-buffer coeff = 27</td>
</tr>
<tr>
<td>Protein binding</td>
<td>95% plasma protein bound (1o α1 acid glycoprotein)</td>
</tr>
<tr>
<td>Intrinsic vasodiilator activity</td>
<td>More vasodilation than ropivavaine (less than lignocaine)</td>
</tr>
<tr>
<td>Isomerism</td>
<td>Racemix mixture 1:1 R and S enantiomers</td>
</tr>
</tbody>
</table>

List brief notes on the physicochemical properties of bupivacaine: PAST QUESTION

1. **Physicochemical properties**

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<tr>
<td>pKa</td>
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<tr>
<td>Isomerism</td>
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</table>

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

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

**Background**
- **bupivacaine** = long acting amide LA
- dose limit for nerve block = 2mg/kg
- plasma [bupivi] threshold for CNS toxicity ~2mg/L
- plasma [bupivi] threshold 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 threshold 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 → 4CO 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
  - Ropivacaine = 4
  - Lignocaine = 7

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

**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

<table>
<thead>
<tr>
<th>LA</th>
<th>Maximum safe dose (mg/kg)</th>
<th>CNS/CVS ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lignocaine</td>
<td>3 without adrenaline</td>
<td>7</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Factors that govern the risk of toxicity include:**
- **Drug factors:**
  - **A:**
    - Rate of absorption into systemic circulation = governed by Fick's law of diffusion
    - Rate of diffusion = \( \frac{area}{thickness} \times \frac{vol}{MW} \times conc \ gradient \)
    - 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
Describe how the chemical structure of local anaesthetic drugs determines their efficacy and safety: PAST QUESTION

**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 structure governs pharmacological properties of La → and therefore efficacy + safety profile

**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 linkage 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 → ↑potency + longer DoA
  - e.g. mepivacaine has methyl substituent on amine tail, bupivacaine has butyl → bup 35x more lipophilic than mepivacaine
- **Chirality**
  - Na+ channel ion is chiral → interaction between LA + Na+ channel demonstrates stereoselectivity
  - E.g. R-dextrobutapicaine ↓potent than S-lebovupicaine → 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 potency**
  - hydrocarbon length of intermediate linkage → lipophilicity → ↑potency → ↑toxicity
  - lipophilic substituents on lipophilic aromatic ring + hydrophilic amine tail → lipophilicity → ↑potency → ↑toxicity
- **Duration of action**
Describe the factors that determine skin penetration of local anaesthetics. Describe the formulation and pharmacology of EMLA: PAST QUESTION

**Background**
- LA = drug which reversibly 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
  - 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 solubility → onset
    - E.g. oil:water partition coefficient of lignocaine = 2.9; prilocaine = 0.9
  - Molecular weight: 1/MW → rate of diffusion
  - Concentration gradient: 1/dose → 1/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 temperature melting point
- **Formulation**
  - 5% white emulsion containing:
    - 2.5% lignocaine
    - 2.5% prilocaine
    - polyoxyethylene fatty acid ester (emulsifier)
    - carbolip (thickening agent)
    - sodium hydroxide (adjusted to pH 9)
    - water
  - melting point of lignocaine = 67°C; prilocaine = 37°C, EMLA = 16°C
- **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 methaemoglobinemia → 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 solubility → ↑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 mucosal
  - obeys Fick’s law of diffusion
  - 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

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Acute cocaine toxicity:

- 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
- Intrinsic vasoconstrictor properties: systemic absorption \( \rightarrow \) DoA; minimise blood loss
- No local site irritation
- No ability to oxidise Hb to form methHb
- Does not cross placenta

Pharmacokinetic:
- Absorption
  - Concentration of active component
  - Buffers: unionised portion \( \rightarrow \) lipid solubility \( \rightarrow \) absorption
  - Low melting point \( \rightarrow \) solubility
  - Low MW \( \rightarrow \) rate of diffusion
  - pKa close to 7.4 (maximal unionised fraction at physiological pH)
  - Lipid soluble \( \rightarrow \) uptake
  - Intrinsic vasoconstrictor activity \( \rightarrow \) systemic absorption \( \rightarrow \) duration of action/ time at target site
- Distribution: PB \( \rightarrow \) VD \( \rightarrow \) duration of action + time at target site
- Metabolism: I metabolism \( \rightarrow \) DoA, high systemic clearance \( \rightarrow \) 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:**

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<tr>
<th>Local toxicity</th>
<th>Dose in mg/kg</th>
<th>Toxic plasma levels</th>
<th>CC/CNS ratio</th>
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</thead>
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<td>Lignocaine</td>
<td>2mg/kg without adrenaline</td>
<td>&gt;5microg/ml</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2mg/kg with adrenaline</td>
<td>&gt;1.5microg/ml</td>
<td>3</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3mg/kg up to 140mg +/− adrenaline</td>
<td>&gt;4microg/ml</td>
<td>5</td>
</tr>
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**Local toxicity**
- High epidural or spinal blockade
  - \( \beta \) 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 \( \rightarrow \) SVR + venous capacitance \( \rightarrow \) MAP + HP
    - Venodilation \( \rightarrow \) VR \( \rightarrow \) HR
    - Blockade of cardioaccelerator (T1-T4) fibres \( \rightarrow \) HR
  - Brainstem block
    - Blockade of resp centre \( \rightarrow \) profound resp depression
    - Blockade of autonomic centre \( \rightarrow \) CVS collapse (MAP + HR)
- Neurotoxicity
  - Epidural/ intrathecal injection \( \rightarrow \) neurotoxicity: mechanism: lignocaine \( \rightarrow \) intracellular [Ca2+] \( \rightarrow \) neurotoxic via unknown mechanism
  - Radicular irritation \( \rightarrow \) transient neurological symptoms that resolve over 1-7 days
  - Cauda equina syndrome \( \rightarrow \) diffuse lumbosacral plexus injury \( \rightarrow \) sensory, bladder + bowel dysfunction, paraparesis
  - Anterior spinal artery syndrome \( \rightarrow \) low limb paresis + dysaesthesia \( \rightarrow \) anterior spinal artery spasm

**Systemic toxicity**
- CNS toxicity
  - Biphasic effect
    - **Excitatory phenomena:** depression of inhibitory interneurons \( \rightarrow \) circumsoral tingling, tongue numbness \( \rightarrow \) restlessness, tinnitus, vertigo \( \rightarrow \) skeletal + facial muscle twitching \( \rightarrow \) seizure
    - CNS depression: depression of central neurons \( \rightarrow \) coma, apnoea
  - Seizure ?2o inhibition of inhibitory GABAergic pathways \( \rightarrow \) unopposed excitatory activities \( \rightarrow \) seizure
- CVS toxicity
  - \( \uparrow \) dose required to produce CVS toxicity than CNS toxicity
  - Main effects: hypotension + bradycardias
  - Mechanism:
    - Cardiac Na channel blockade LAs \( \rightarrow \) slow conduction of cardiac impulses \( \rightarrow \) PR prolongation + QRS widening \( \rightarrow \) 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 \( \uparrow \) vulnerable to LA than CVS
- Hypersensitivity reaction
  - Rare
  - LA or additive can \( \rightarrow \) hypersensitivity reaction
  - Ester LAs metabolised to para-aminobenzoate (Trates allergy)
- Hepatotoxicity
  - Continuous epidural infusion of bupivacaine found to rarely cause hepatic enzyme derangement + hepatotoxicity
  - Mechanism unclear
- Methaemoglobinemia
  - Prilocaine metabolised in liver to o-toluidine \( \rightarrow \) oxidises Fe2+ of haem to Fe3+ \( \rightarrow \) methaemoglobin (unable to carry O2) \( \rightarrow \) tissue hypoxia

**Extrav 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

**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 (TPB → free drug → toxicity)
- Intrinsic vasodilator activity

**Patient factors**
- Acidosis → ionised → ion trapping → ↑toxicity
- Pregnancy → ↑progesterone → competitive binding to AAG → ↑unbound LA → ↑toxicity
- 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 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 boluses. 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
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 beam 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 puncture)

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 intraneural 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
Continuous regional anaesthesia: MAKEUP

CRA:
- catheter placed near a nerve or plexus \(\rightarrow\) LA injected or infused down catheter for hours –days postop
- early mobilisation; \(\uparrow\) 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**
- \(\uparrow\) speed of onset of conduction blockade
- \(\uparrow\) susceptibility to LA toxicity (\(\uparrow\) progesterone \(\rightarrow\) \(\uparrow\) tissue sentivity + \(\downarrow\) PB \(\rightarrow\) \(\uparrow\) free fraction)
- \(\downarrow\) dose required in spinal/ epidural due to engorged epidural vascular plexus
- Factors improving LA use in mother:
  - Degree of cardiotoxicity
    - Bupivacaine = \(\uparrow\) cardiotoxic than ropivacaine
    - Ropivacaine toxicity \(\uparrow\) in pregnancy: CC:CNS ratio \(\downarrow\) from 3 to 2 in pregnancy = unsafe
  - Degree of CNS toxicity
  - Motor function preserved: ropivacaine affects Adelta + C fibres > motor fibres \(\rightarrow\) better
  - Method of metabolism: esters metabolised by plasma esterases which \(\uparrow\) in pregnancy

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

**Normal practice in obstetrics**
- ropivacaine preferred agent for epidurals: relative sparing of motor block; low foetal:maternal ratio, \(\downarrow\) risk toxicity
- bupivacaine good for intrathecal route
## Central Neuraxial Blocks

### Spinal

<table>
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<tr>
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<td>Spinal</td>
<td>LA +/- adjunct injected into subarachnoid space Subarachnoid space: extends laterally along the nerve roots to the dorsal root ganglia; continuously with intracranial subarachnoid space</td>
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<td>Details</td>
<td>Lower abdo / perineal surg; LE; LSCS, NB due to segmental nature, may be suboptimal for sacral distribution To lesser extent analgesia provided by diffusion into subarachnoid space</td>
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<tr>
<td>Quality</td>
<td>LA +/- adjunct injected in epidural space Epidural space = potential low pressure space that lies between the walls of the vertebral canal + spinal dura mater</td>
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<td>Advantages</td>
<td>Ability to produce segmental block Greater control over analgesia Possibility of long term analgesia</td>
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<tr>
<td>Contraindication</td>
<td>Relative: aortic/ MV stenosis (4BP 2o SY block) hypovolaemia (4BP) previous back surgery neuro disease: TICP systemic sepsis (risk abscess/ meningitis) platelets &lt;80</td>
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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

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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 = 1° 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

NB: Anything above T5 inhibits SNS to GIT
Central neuraxial analgesia and anticoagulants: MAKEUP

- Aspirin and NSAIDs
  - No contraindications

- Clopidogrel
  - Stop 7 days before neuraxial block

- UFH:
  - Subcut VTE
    - doses seldom associated with 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. licensed 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 ropivacaine 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)

<table>
<thead>
<tr>
<th>LA</th>
<th>pKa</th>
<th>PB %</th>
<th>Max dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Features</th>
<th>Intrathecal/ epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lignocaine</td>
<td>7.9</td>
<td>70</td>
<td>3mg/kg</td>
<td>Fast</td>
<td>Medium: 60-90mins</td>
<td>Moderate vasodilatation, cerebral irritation before CC, good sensory + motor block, favourable recovery profile, good for short spinal procedures</td>
<td>Epidural, Not for spinal due to risk of cauda equina syndrome + transient radicular irritation/ transient neuro sx</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>95</td>
<td>2mg/kg</td>
<td>Medium</td>
<td>Long</td>
<td>Good sensory, less motor block, better for longer duration spinal/ long lasting post op analgesia, prolonged cardiotoxicity in ↑ doses</td>
<td>Both</td>
</tr>
<tr>
<td>Ropicavaine</td>
<td>8.1</td>
<td>95</td>
<td>3mg/kg</td>
<td>Medium</td>
<td>Long</td>
<td>Less likely to produce LA toxicity cf</td>
<td>Epidural</td>
</tr>
</tbody>
</table>
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

**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

**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
  - Alkalisation 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 of 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**
**Cardiovascular response to central neuraxial block**

**Overview:**
- Central neuraxial block achieved by: subarachnoid (spinal) or epidural
- LA (bupivacaine, ropivacaine) +/- opioid (fentanyl, morphine)
- Effects are more pronounced in:
  - Elderly (4 physiological reserve)
  - Fixed cardiac output states
  - ↓ blood volume

**CVS response**
- NB neuraxial block result in sympathetomy-2-6 dermatomes above the sensory block
- ↓ MAP due to:
  - Blockade of α and 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:
    - Bainbridge reflex: stimulation of RA stretch Rs → ↓VA afferent stimulation of medulla → ↑PSY activity → ↓HR
    - Direct effect on SA node by atrial stretching
    - Anaesthesia of T1-4 cardioacceleratory 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 of RAAS by ↓afferent arteriolar stretch
  - “High block”: T1-T4 cardioacceleratory centre → blockade → unable to ↑HR/contractility with SNS stimulation
  - Brainsstem 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 RAAS/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:
  - ↓ tone of resistance vessels (↓SVR) + ↓VR to heart → ↓CO

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

<table>
<thead>
<tr>
<th>Sympathomimetic</th>
<th>Mechanism</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>Direct α1+β1</td>
<td>Drug of choice for high spinal</td>
<td>Arrhythmogenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rapid onset</td>
<td>↑HR → ↑CMRO2 → may precipitate ischaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No tachyphylaxis</td>
<td>needs CVC</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>↑NAd release</td>
<td>Drug of choice for obstetric (doesn’t affect uterine BF)</td>
<td>Tachyphylaxis</td>
</tr>
<tr>
<td></td>
<td>↑NAd reuptake</td>
<td>Compatible with PIVC access</td>
<td>Foetal acidosis</td>
</tr>
<tr>
<td></td>
<td>inhibit MAO</td>
<td>Longer DoA</td>
<td>Arrhythmogenic</td>
</tr>
<tr>
<td></td>
<td>indirect α1+ β1</td>
<td>Not metabolised by MAO/ COMT</td>
<td>Renal excretion</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Direct α1</td>
<td></td>
<td>Reflex ↓HR→ not appropriate for high spinal</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Direct α1</td>
<td>PIVC</td>
<td>↑CMRO2</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>Direct α1</td>
<td></td>
<td>extravasation → tissue necrosis</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>Direct B1</td>
<td></td>
<td>As above</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Direct B1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>B1 low dose</td>
<td>Less arrhythmogenic vs. adrenaline</td>
<td>Difficult to titrate between dose effects</td>
</tr>
<tr>
<td></td>
<td>α1 high dose</td>
<td></td>
<td>More arrhythmogenic vs. NAd</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>V1</td>
<td>Non-adrenoceptor pathways → useful in pts who are B blocked</td>
<td>Coronary artery vasoconstriction → can precipitate ischaemia</td>
</tr>
</tbody>
</table>

- common features of agents
  - pharmaceutical presentation: all require dilution before use
  - agents with strong vasoconstricting effect have risk of tissue necrosis if extravasation occurs
  - risk of HTN
  - can cause tachycardia via direct effects or reflex bradycardia

- Relevant patient problems that contribute to advantages/ disadvantages:
  - Age/ intercurrent illness esp. cardiovascular disease + antihypertensive meds
  - Pregnancy + childbirth
  - Drug interactions i.e. MAOI

**Regional and local anaesthesia**

- Vasopressin
- Dopamine
- Adrenaline
- Noradrenaline
- Ephedrine
- Metaraminol
- Phenylephrine
- Isoprenaline
- Dobutamine
- Vasopressin

**Goals of pharmacological rx:**
- Mechanism:
  - α1
  - β1 low dose
  - β1 high dose
  - β2
  - α1
  - Non-adrenoceptor pathways
  - Non-adrenoceptor pathways

- Agent 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
- 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 SV 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 + horns + phrenic nerve paralysed → apnoec
  - 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

<table>
<thead>
<tr>
<th>Pattern of failure</th>
<th>Remedy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global failure</td>
<td>Resite epidural</td>
</tr>
<tr>
<td>Partial failure</td>
<td>Top up epidural with painful side in dependent position</td>
</tr>
<tr>
<td>Unilateral block</td>
<td>- Use LA + 50-100microg fent</td>
</tr>
<tr>
<td></td>
<td>- Withdraw catheter 2-3cm and give further top up</td>
</tr>
<tr>
<td>Missed segment</td>
<td>- top up with opioid e.g. 50-100microg fent → intrathecal MoA will</td>
</tr>
<tr>
<td></td>
<td>- ↓segmental effects</td>
</tr>
<tr>
<td>Back pain</td>
<td>- continue as per unilateral block</td>
</tr>
<tr>
<td>Perineal pain</td>
<td>- top up with more LA and opioid</td>
</tr>
<tr>
<td></td>
<td>- check sacral block and that bladder is empty</td>
</tr>
<tr>
<td></td>
<td>- top up with more LA in sitting position</td>
</tr>
<tr>
<td></td>
<td>- continue as per unilateral block</td>
</tr>
</tbody>
</table>

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
Describe the dermatomal + myotome innervations

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

* Commonly tested reflexes

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

Prerequisites
- 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 distorts 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 + vaspressors
- HR: bradycardia can occur due to unopposed VA cardiac stimulation if SV 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