Ho Medical
ANAESTHESIA

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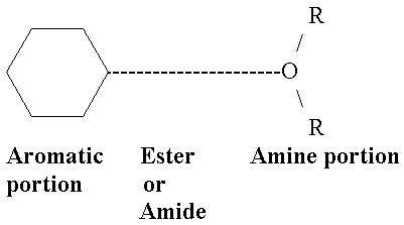
Local Anaesthetics

Pharm-10A1/93 Describe how the chemical structure of local anaesthetic drugs determines their efficacy and safety.

1. Local anaesthetic drugs – weak bases. Their structure-activity relationships depend on 2 major factors:
    a. Class: amides and esters.
        i. Amides –
            1. amide group links the hydrophilic and aromatic groups
            2. bupivacaine, ropivacaine, lignocaine, prilocaine
        ii. Esters –
            1. ester group links the hydrophilic and aromatic groups
            2. procaine, tetracaine, amethocaine



    b. Ionisation: Local anaesthetics are weak bases, which exist in equilibrium between an unionised (lipophilic) form and an ionised form (protonated). The unionised form penetrates the neuronal cell membrane, where it becomes protonated in the axoplasm. The protonated form is able to bind to the Na channel and block it. The degree of ionisation is important and depends on pKa with respect to the tissue environment –

$$LA + H^+ \Leftrightarrow LAH^+$$

    Since local anaesthetics are bases with high pKa, in general, ↑pKa → ↑ fraction ionised form → less penetration.

    c. Chemical structure:
        i. ↑ aromatic side chain length → ↑ lipid solubility, protein binding
            1. Butyl group + procaine → amethocaine
        ii. ↑ amine side chain length → ↑ lipid solubility, protein binding
            1. Lignocaine, prolocaine
        iii. Bupivacaine butyl side chain > ropivacaine propyl side chain > mepivacaine methyl side chain.
    d. Enantiomers: amide anaesthetics have enantiomers (optical isomers), of which different isomers confer different properties. In general, S-enantiomers are more potent and less toxic compared to the R-enantiomer (bupivacaine).

2. Efficacy: local anaesthetics block fast Na channels in peripheral nerve fibres, and hence block the transmission of the action potential.

Drug	pKa	% unionised	Protein	$T_{1/2}$	Onset	Duration	Lipid Sol	Potency
Amethocaine	8.5	7	75	80	slow	long	200	8
Procaine	7.7	33	55	100	Fast	moderate	50	2
Lignocaine	7.9	25	70	100	Fast	moderate	150	2
Ropivacaine	8.1	15	95	120	moderate	Long	300	8
Bupivacaine	8.1	15	94	160	Moderate	long	1000	8

    a. Pharmacokinetics:
        i. Absorption:

1. The absorption of drugs at site of action is determined by the degree of unionised drug. As above:
   ↓pKa → more unionised drug → greater penetration
   ↓ tissue pH (inflammation → acidosis) → less unionised → less penetration

ii. Distribution:
1. Lipid solubility: Lipophilic drugs are absorbed more quickly and readily by the axoplasm and hence have a faster duration of action. In general, local anaesthetics with longer side-chains confer greater lipid solubility.
2. Protein binding: only free drug can exert therapeutic action, so drugs with ↑ protein binding → less penetration → ↑ duration action.
   Ester anaesthetics are minimally bound compared to amides and have shorter duration action.
3. Vasodilation: drugs which cause vasodilatation → ↑ blood flow → ↓ potency / duration of action.
   a. Prilocaine > lignocaine > bupivacaine > ropivacaine

iii. Metabolism
1. Ester drugs: metabolised by plasma cholinesterases → inactive compounds including para-aminobenzoate. Hence, generally have a short half-life and duration of action, not dependent on liver function.
2. Amide drugs: metabolised in the liver by amidases → slower elimination affected by liver function.

3. Safety:
   a. Pharmaceutical shelf-life:
      i. Esters unstable in solution, shorter shelf life
      ii. Amides stable in solution, shelf life 2 years.
   b. Specific organ toxicity
      i. CVS – local anaesthetics also bind to cardiac myocyte Na channels. Duration of binding confers toxicity → ↑ PR, QRS intervals, refractory periods.
         ↑ lipid solubility, potency → ↑ duration binding to cardiac Na channels → ↑ toxicity
      ii. CNS – blocks Na channels in CNS neurons → biphasic effects with initial excitatory phenomenon followed by CNS depression.
         ↑ lipid solubility, ↑ protein binding → ↑ BBB penetration and duration of action → ↑ CNS toxicity
   c. Materno-foetal – protein bound drugs cannot cross placenta. ↑ protein binding → less feto-toxic.
      Ester drugs are metabolised quickly and generally do not cross the placental barrier.
   d. Hypersensitivity – esters are more likely to cause hypersensitivity reactions in atopic individuals because plasma cholinesterases produce para-aminobenzoate.

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Pharm-09A2/07B5 Describe the factors which increase the risk of systemic toxicity with amide local anaesthetic agents.

1. Amide local anaesthetics: generally, systemic toxicity is closely related to abnormally high plasma concentration of a local anaesthetic drug. This differs according to Pharmacodynamic, pharmacokinetic drug properties and patient factors. In general, guidelines for maximum safety doses are as follows:

Drug	Maximum safe dose (mg/kg)	CC/CNS ratio
Prilocaine	6	
Lignocaine	3	7
Ropivacaine	2	5
Bupivacaine	2	3

2. Toxicity: The main toxicities are organ related – CNS, CVS, and foetal. Local anaesthetics have a CC/CNS ratio, which describes plasma conc required to cause CV collapse vs plasma conc required to cause CNS symptoms. Lower ratio → ↑ toxicity.
    a. CVS: amide local anaesthetics bind to cardiac myocyte fast Na channels and block them in their inactivated state. They act as type Ib anti-arrhythmics, prolonging RP, PR and QRS intervals.
    b. CNS: bind to CNS neuron Na channel producing biphasic effect –
        i. Initial excitation – twitching, convulsions
        ii. Delayed depression – coma, respiratory depression
    c. Feto-maternal: can cross the placental barrier and cause above effects to foetus.

[Lignocaine] µg/mL	Toxicity
4	Light-headed, tinnitus, tongue numbness
6	Visual disturbance
8	Muscle twitching
10	Convulsions
12	Unconsciousness
15	Coma
20	Respiratory arrest
26	Cardiovascular collapse

3. Drug factors:
    a. Pharmacokinetic:
        i. Absorption: ↑ systemic absorption → ↑ toxicity
            1. Site: ↑ blood flow to site → ↑ toxicity.
            Intrapleural > intercostals > pudendal > caudal > epidural > brachial plexus > subcutaneous
            2. Vasodilator: local anaesthetics cause vasodilation at low doses → ↑ toxicity.
            Prilocaine > lignocaine > bupivacaine > ropivacaine
            3. Vasoconstrictor: addition of adrenaline → local vasoconstriction → ↓ systemic toxicity.
            Lignocaine max dose 3mg/kg, lignocaine + adrenaline 7mg/kg
        ii. Distribution: local anaesthetics are bases with high pKa, which exist in the equilibrium - $LA + H^+ \Leftrightarrow LAH^+$
        The unionised form is more lipid soluble and required to get to site of action. However, the ionised form binds to the Na channel and blocks it. Usually, the

unionised LA crosses into the cell cytoplasm where it is protonated to exert its effect.
Drugs with lower pKa → greater % unionised at body pH 7.4 → ↑ lipid solubility
Lignocaine pKa 7.9 25% unionised pKa 7.4
Bupivacaine 15% pKa 8.1 unionised pKa 7.4

1. Lipid solubility: ↑ lipid solubility → ↑ penetration into cardiac, CNS cells → ↑ toxicity
2. Protein binding: ↓ protein binding → ↑ free drug available for systemic toxicity.
3. Ion trapping: drugs with higher pKa → more ionised in acidic environments (metabolic acidosis of cardiac arrest, inflammation) → trapping of drug inside acidic cells → ↑ toxicity

iii. Metabolism: amides are metabolised into less toxic products by liver amidases.
1. Liver function - ↓ liver function (hepatic failure) → ↑ toxicity
2. Active metabolites – some metabolites may be partially active and cause toxicity (3-OH ropivacaine)

b. Pharmacodynamic:
i. Dose, Concentration: ↑ dose/concentration → ↑ plasma conc → ↑ toxicity
ii. Drug interactions:
1. Protein binding: protein displacement → ↑ free drug → ↑ toxicity
2. Other anti-arrhythmics: synergistic cardiac toxicity
3. Enzyme inhibition: ↓ metabolism → ↑ toxicity (cimetidine)
iii. Drug-receptor interaction: ↑ Na channel affinity cardiac myocytes → ↑ toxicity (bupivacaine > ropivacaine)
iv. Isomerism: pure enantiomers have a better safety profile than racemic mixtures. Generally S-enantiomers safer than R-enantiomers.

4. Patient factors:
a. Disease
i. Cardiac failure - ↓ VD, ↑ acidosis, ↑ sensitivity to cardiac depression → ↑ toxicity
ii. Acidosis – ion trapping at CNS, CVS → ↑ toxicity
b. Pregnancy
i. ↑ p
c. Age:
i. ↓ VD → ↑ risk toxicity (loading dose produces ↑ plasma concentration)
d. Organ failure:
i. Liver failure → ↓ protein production, ↓ metabolism → ↑ toxicity
ii. Renal failure → ↓ elimination of active metabolites

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Pharm-02A9/99B11 *Outline the toxicity of local anaesthetics.*

1. Toxicity is defined as the deleterious side-effects of a drug. Local anaesthetics have toxicity which can be classified as local (excessive blockade) or systemic (blockade of non-target sites).

2. Local toxicity:
    a. Sympathetic chain blockade – epidural or spinal blockade blocks sympathetic pre-ganglionic fibres (type B), which are more readily blocked than type A fibres. SNS blockade produces varying degrees of autonomic dysfunction depending on level of spinal cord.
        i. High thoracic → uncompensated ↓ MAP, CV collapse
        ii. Low thoracic → ↓ MAP< tachycardia with baroreceptor reflex
    b. Neurotoxicity – lignocaine most risk
        i. Radicular neuronitis
        ii. Cauda equina – inappropriate blockade lumbosacral plexus → bilateral leg paraesthesia, weakness, bladder/bowel dysfunction
        iii. Anterior spinal artery syndrome – thrombosis/spasm of anterior spinal artery

3. Systemic toxicity: follows a usual progression and symptoms/signs and is related to plasma concentrations. This is best characterised by lignocaine:

[Lignocaine] µg/mL	**Toxicity**
4	Light-headed, tinnitus, tongue numbness
6	Visual disturbance
8	Muscle twitching
10	Convulsions
12	Unconsciousness
15	Coma
20	Respiratory arrest
26	Cardiovascular collapse

    a. CNS – biphasic response (as above):
        i. Initial excitatory phenomena due to inhibition of inhibitory pathways. Plasma conc = 5-10µg/mL
        ii. Later depression phenomena due to inhibition of all pathways. Plasma conc > 10µg/mL
    b. CVS – bupivacaine > ropivacaine > lignocaine.
        i. Depressed conductivity: ↑ PR, QRS interval, ↑ refractory period
        ii. ↓ systemic vascular resistance, contractility
        iii. Persistent binding to myocardial channels high doses → VT/VF
    c. Allergy –
        i. Esters - more likely with esters due to production of PABA.
        ii. Amides – rare, but usually due to additives metabisulphite and methylparaben

4. Specific toxicity:
    a. Cocaine – ester LA, medium acting, derived from plant
        i. ↓ reuptake NA → CNS excitatory, seizures; CVS - ↑ HR, BP, MAP
        ii. Potent vasoconstriction → CVS coronary a spasm, AMI; local ischaemia and necrosis
    b. Prilocaine – amide LA, short-acting

i. Methaemoglobinaemia – metabolised in liver to o-toludine → oxidises Fe^{2+} → Fe^{3+} causing Hb → MetHb. MetHb cannot carry O2 and is blue in colour → conc > 10mg/mL (50%) → cyanosis. Susceptible groups are neonates and congenital enzyme deficiencies (PK, G6P deficiencies) who have ↓ methaemoglobin reductase.

5. Factors affecting toxicity: systemic toxicity is directly related to plasma concentration of drug. This is influenced by pharmacodynamic, pharmacokinetic and patient factors.
    a. Administration factors:
        i. Dose / concentration: toxicity in related to the peak plasma concentration and also the rate of rise of plasma concentration. ↑ dose / ↑ conc → ↑ toxicity.
        ii. Local site: ↑ vascularity → ↑ systemic absorption
        Highest risk intrapleural > intercostals > caudal > brachial plexus > SC > TOP
        iii. Additives:
            1. Adrenaline – local vasoconstriction → ↓ blood flow → ↓ systemic uptake → ↓ toxicity (more so for drugs which cause vasodilation
            2. Other local anaesthetics – synergistic effect
    b. Drug factors:
        i. Lipid Solubility: the primary determinant of potency, which affects the threshold plasma concentrations at which toxicity occurs for different drugs:

Drug	Threshold for toxicity µg/mL	Haptane:buffer
Bupivacaine	1.5	28
Ropivacaine	4	
Lignocaine	5	2.9

        ii. Vasoactivity: drugs causing vasodilation low doses → ↑ blood flow → ↑ toxicity
        Prilocaine > lignocaine > bupivacaine > ropivacaine
        iii. Protein binding: only free drug is active, thus ↑ protein binding → ↓ free drug that can penetrate tissues.
        States protein binding (pregnancy, liver failure) → ↑ toxicity
        iv. Isomerism: bupivacaine and ropivacaine are enantiomers in which R-enantiomer is more toxic than the S-enantiomer.
        Ropivacaine (pure S-) safer than bupivacaine (1:1 racemic mixture)
        v. Metabolism / Clearance: ↑ clearance → ↓ plasma conc → ↓ toxicity
            1. Esters: metabolised by pseudocholinesterase in plasma and peripheral tissues → quick metabolism → ↓ systemic toxicity.
            Except cocaine which is hepatically metabolised → ↑ likelihood CNS/CVS toxicity
            2. Amide: metabolised in liver → longer half-lives → more likelihood of plasma accumulation.

Drug	Clearance L/min
Bupivacaine	0.47
Ropivacaine	0.82
Lignocaine	6.8-11.6

    c. Patient factors:
        i. Acidosis – acidic environments → ↑ionised portion → cannot escape through lipid membrane for distribution → ↑ toxicity of organs where trapping occurs.
        ii. Pregnancy – progesterone competes with α_1 acid glycoprotein → ↑ free drug → ↑ toxicity

iii. Disease states: cardiac / hepatic / renal failure → ↓ metabolism and elimination → ↑ toxicity
iv. Obesity: fat acts as reservoir for lipid soluble drug → ↓ systemic toxicity
v. Electrolytes: ↑ K, ↓ Ca → hyperexcitable membrane → ↑ toxicity

Pharm-06A5/03B7/00B13/95 Write short notes on factors affecting the speed of onset and duration of effect of local anaesthetics when used to produce peripheral nerve block.

1. Local anaesthetics are drugs which block peripheral nerve action potentials used for regional anaesthesia.
    a. Mechanism: LA + H^+ ⇔ LAH^+. LAs enter the neuron axoplasm in their unionised lipid soluble form. Inside, they are protonated (ionised), and this form binds to the NA channel receptors to block them in the inactive state.
    b. Fick's equation: the speed of onset, and duration of action depend on the amount of active drug that reaches the target site. Factors can be explained using Fick's law of diffusion –

$$\textbf{Diffusion} = \frac{\textbf{Sol x A x } \Delta\textbf{P}}{\sqrt{\textbf{MW}}\textbf{xT}}$$

2. Drug factors
    a. Absorption: areas with ↑ blood flow → redistribution of drug → ↓ concentration at site → ↓ duration action
        i. Site action:
            1. Nerve infiltration quicker speed of onset than topical or subcutaneous injection (direct injection into site of action, less diffusion required)
        ii. Area: ↑ area application → ↑ degree blockade (requires 3 nodes Ranvier for block)
        iii. Thickness: application of local anaesthetic closer to nerve → ↑ onset action
        iv. Vascularity:
            1. Vasodilate: some LAs cause dilation at low doses → ↑ systemic absorption → ↓ duration action. (prilocaine > lignocaine > bupivacaine > ropivacaine)
            2. Vasoconstrict: administration with adrenaline → vasoconstriction → ↓ systemic absorption → ↑ duration action
    b. Distribution: smaller, lipid soluble drugs cross lipid membranes more easily → ↑ solubility → ↑ speed onset
        i. Protein binding: binding with α acid glycoprotein/albumin in equilibrium. Only unbound drugs can act, be metabolised
            1. ↑ protein binding → ↑ duration action (bupivacaine 94% > lignocaine 70%)
        ii. Drug pKa: LAs are weak bases
            1. ↓pKa → ↑ unionised portion at body pH → ↑ solubility → ↑ speed onset
        iii. pH: ionised local anaesthetics can become trapped inside cells once at site of action → ↑ duration
            1. ↑pKa → ↑ ionisation in acidic environments (inflammation, acidosis) → ↑ duration of action (bupivacaine in acidosis) "ion trapping"
            2. Addition bicarbonate → ↑pH → ↑unionised portion → ↑ lipid solubility → ↑ speed onset
    c. Metabolism

i. Peripheral vs. Hepatic:
    1. Esters – metabolised by plasma and non-specific tissue cholinesterases into inactive metabolites → ↓ duration action (↓ concentration)
    2. Amides – metabolised by hepatic amidases
ii. Active metabolites: some amides (ropivacaine → 3-OH ropivacaine) have active metabolites → ↑ duration action

d. Pharmacodynamic
i. Concentration / dose:
    1. ↑ dose/conc → ↑ conc gradient → ↑ diffusion → ↑ speed onset / duration action
ii. Drug-receptor interaction:
    1. ↑ affinity for Na-channel (eg bupivacaine > ropivacaine for Na channels) → ↑ duration of action:
iii. Drug-drug interaction:
    1. Protein binding competition → displace LAs from protein binding → ↑ free drug → shorter duration action
    2. Hepatic inhibition/induction:
        a. Inhibition (cimetidine) → ↓ metabolism → ↑ duration action
        b. Induction (phenytoin) → ↑ metabolism → ↓ duration action

3. Patient factors
a. Nerves:
i. Size – larger nerves require ↑ doses for blockade (thicker diffusion distance)
ii. Myelination – myelinated nerve blocked before non-myelinated
iii. Activity – nerve firing preferentially blocked (inactivated state)
iv. Position – central nerve ↓ speed onset, but ↑ duration

b. Disease states:
i. Acidosis - ↓ pH → ↑ ionised drug → ↓ lipid solubility → ↓ speed of onset (can't penetrate into cell membrane)
ii. Electrolyte –
    1. ↑ K, Mg → ↑ excitability → ↑ speed onset
    2. ↑ Ca → ↓ excitability → ↓ speed onset

c. Physiological states
i. Pregnancy → progesterone → faster onset action
ii. Age: young ↓ α_1 acid glycoprotein

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Pharm-04A3/00A16 Briefly describe the factors that determine skin penetration of local anaesthetics. Briefly describe the formulation and pharmacology of EMLA cream.

1. Local anaesthetics can be applied topically to block sensory nerves subcutaneously. This is used in the epithelium, mucous membranes, airways, conjunctiva and tympanic membrane. This therapeutic action requires diffusion of the drug through the epidermis, the neuron cell membrane, to its site of action – the cytoplasmic side of the fast Na channels.

2. The factors that determine skin penetration can be summarised according to Fick's law of diffusion:

$$\textbf{Diffusion} = \frac{\textbf{Sol x A x } \Delta\textbf{P}}{\sqrt{\textbf{MW}}\textbf{xT}}$$

   a. Area: ↑ surface area applied → ↑ total diffusion of drug, ↑ area of anaesthesia. However, no affect on focused anaesthesia of specific neurons, so ↑ area does not benefit if small area anaesthesia desired.
   b. Thickness:
      i. ↑ thickness s membrane → slower / less diffusion
      ii. ↑ distance to epidermal neuron → slower/less diffusion
   c. Solubility: unionised forms of the local anaesthetic are soluble, ionised are not
      i. Structure – solubility relationship:
         1. ↑ intermediate chain length → ↑ solubility
         2.
      ii. pKa – since local anaesthetics are weak bases, those with lower pKa will be more unionised in body pH 7.4, hence more soluble:
         1. prilocaine pKa 7.7 → 33% unionised, bupivacaine pKa 8.1 → 15% unionised
      iii. tissue pH: acidic environments (acid burns) → ↑ ionised portion → solubility → ↓ effect
      iv. additive: sodium bicarbonate added to ↑ solubility
   d. Concentration gradient:
      i. Concentration drug: ↑ conc → ↑ gradient → ↑ diffusion
      ii. Dose: ↑ dose → ↑ gradient → ↑ diffusion
      iii. Pharmaceutical preservatives: ↑ shelf-life / stability → ↑ conc active drug
      iv. Blood supply:
         1. ↑ blood supply skin → ↑ uptake systemic circulation → ↓ activity of drug at local site
         2. Adrenaline added → vasoconstriction → ↓ systemic uptake → ↑ local effect

3. Eutectic mixture: a mixture of 2 agents at a ratio in which the melting point is below that of the individual component melting points. In local anaesthetics, this allows cream formulation which ↑ solubility on topical application.
   EMLA = eutectic mixture of local anaesthetics.
   a. Pharmaceutical:
      i. Contains: 2.5% lignocaine, 2.5% prilocaine, arlatone (emulsifier), carbopol (viscosity), water (1g), NaOH (↑pH)
      ii. EMLA MP = 16, lignocaine 37, prilocaine 67
   b. Pharmacodynamics:
      i. Use: topical anaesthetic cream applied over epithelium (not over broken skin) for venepuncture, cannulation, skin graft donor sites.

ii. Mechanism:
    1. Lignocaine and prilocaine diffuse into epidermis
    2. Block fast (Aδ) and slow (C) pain fibres (unionised portion)
    3. Acidic cytoplasm protonates drug → ionised form binds to Na channels and blocks them in open-inactive state (rate-dependent block) → prevents propagation of APs → blocks nociception
iii. Application:
    1. Thick layer applied over skin target area with occlusive dressing
    2. Water swells stratum corneum → ↑ vascularity → ↑ absorption
iv. Toxicity:
    1. Local – skin irritation, allergy uncommon
    2. Systemic: unlikely if used on intact skin, toxicity depends on abnormal concentration of lignocaine/prilocaine in systemic circulation (dependent on pharmacokinetic variables). Therefore, EMLA is not applied to mucous membrane or broken skin.
        a. Lignocaine: >4mg/L → CNS effects (light-headed, numbness)
        b. Prilocaine:
            i. Liver metabolism → o-toludine → oxidises Hb → MetHb
            ii. Methaemoglobinaemia in groups who can't reduce Met-Hb → Hb (neonates, congenital metHb)
            iii. Treatment with reducing agents: sodium thiocyanate, hydroxycolubamin, methylene blue

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Pharm-01B11/97B10/91 Describe the required pharmacological characteristics of local anaesthetic formulations intended for topical use.

1. Topical local anaesthetics: agents which block neuronal impulses and are used on the skin and mucous membranes to block transmission of nociceptive fibres for procedures / analgesia. For this use, ideal properties of local anaesthetic agents are divided into pharmaceutical, pharmacokinetic, and pharmacodynamic.
    a. Use:
        i. Skin – cannulation, venepuncture, phlebotomy
        ii. GU tract – IDC
        iii. Mucous membranes GI tract – ulcers, oral procedures, reflex, tonsillitis
        iv. Conjunctiva – examination

2. Pharmaceutical:
    a. Inexpensive, easy formulation
    b. Easy to apply – low melting points allow cream/viscous formulations to be applied more easily → ↑ absorption
    c. Long shelf-life – stability in storage → ↑ active ingredient
    d. Multiple preparation available: for use on different membranes → gels, creams, ilquids, sprays, ointments, lozenges
    e. Additives:
        i. High solution pH → ↑ unionised portion of drug → ↑ lipid solubility → ↑ potency
        ii. Vasoconstrictor (adrenaline) → ↓blood flow locally → ↓ systemic absorption 1/3 → ↓ toxicity and ↑ local concentration

3. Pharmacokinetic:

$$\textbf{Diffusion} = \frac{\textbf{Sol x A x } \Delta\textbf{P}}{\sqrt{\textbf{MW}}\textbf{xT}}$$

    a. Well absorbed / rapid onset:
        i. Lipid soluble:
            1. pKa – lower pKa → more unionised at body pH → ↑ absorption, speed onset
            2. additives to ↑pH: bicarbonate is added to ↑ pH → ↑ unionised portion of drug → ↑ solubility, speed onset
        ii. Concentration gradient: sufficient concentrations of drug required in formulation
    b. Long duration action:
        i. ↓ systemic absorption → ↑ duration action
            1. Local anaesthetics have dilating effect low doses (prilocaine > lignocaine > bupivacaine) → ↑ systemic absorption
            2. Adrenaline 1:20000 (0.05%) added to constrict → ↓ absorption → ↑ duration action, ↓ toxicity
        ii. ↑ protein binding → ↑ duration action
    c. Metabolism: ↑ systemic clearance desirable → prevents systemic toxicity
        i. Chemical structure –
            1. esters rapidly metabolised by plasma cholinesterase → ↓ duration action, but ↓ build-up of drug → ↓ toxicity
            2. amides hepatic metabolism → ↑ duration of action, but ↑ likelihood of systemic toxitiy

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   ii. Inactive metabolites preferable → ↓ toxicity:
      1. Prilocaine → o-toludine → methaemoglobinaemia

4. Pharmacodynamic:
   a. Potent:
      i. Adequate drug-receptor effect: drug appropriately blocks Na channels in neuronal cell membrane at concentration in formula.
      ii. Potency related to lipid solubility
   b. Minimal local side effects:
      i. Minimal skin irritation
      ii. Minimal hypersensitivity – esters metabolised → paraaminobenzoic acid (PABA) → ↑ risk hypersensitivity
      iii. Problem with vasoconstriction for cannulation
   c. Minimal systemic side-effects: systemic side effects related to abnormally high conc plasma:
      i. Vasoconstrictor properties are desirable
      ii. Vasodilation properties undesirable
      iii. High therapeutic ratio

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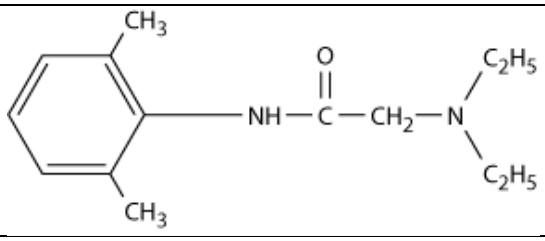
Pharm-05B3/96B13 Write brief notes on the pharmacology of lidocaine (lignocaine).

1. Lignocaine is an amide local anaesthetic drug used for the conduction blockade of nerve fibres. It is used commonly in anaesthetic for topical, regional, subcutaneous and epidural nerve blockade.

Physiochemical	
Structure	
Group	Amide local anaesthetic
Structure-activity	1. Amide linkage is metabolise by hepatic amidases (requires hepatic function, longer $T_{1/2}$ compared to esters which are metabolised peripherally) 2. Ethyl side chains on hydrophilic tail, and methyl groups of aromatic ring → ↑ lipid solubility → ↑ potency
Isomerism	None
Formulation	Solution 0.5-2% – SC Topical solution 4% Gel 2% Ointment 5% Aerosol EMLA – 2.5% emulsion with 2.5% prilocaine
Shelf-life	Long shelf-life
O:W Lipid solubility	2.9 10 x less lipid soluble than bupivacaine → ↓ potency, ↓ toxicity
pKa	7.9
% unionised	25% at pH 7.4. < prilocaine 33%, > bupivacaine 15% A greater unionised portion → ↑ diffusion into cell membrane → ↑ speed onset / potency
Protein binding	70% to α_1 acid glycoprotein Protein binding → ↓ systemic absorption → confers ↑ duration action
Additives	Adrenaline → vasoconstriction → ↓ systemic absorption, ↑ duration action Na2CO3 → ↑pH → ↑ unionised portion → ↑ lipid solubility
Pharmacokinetic	
Absorption	PO: F = 40%, extensive 1st pass metabolism SC/topical relates to Fick's diffusion factors: F = (AxsolxΔP)/(√MW x T) ↑ absorption with ↑ area applied, ↑pH environment, ↑ conc/dose applied, ↓ thickness to systemic vessels. Site: ↑ absorption intrapleural > intercostal > caudal > epidural > brachial plexus > SC
Distribution	O:W 2.9 → low lipid solubility → ↓ potency Protein binding 70% → confers ↑ duration of action VD = 1L/kg
Metabolism	Hepatic dealkylation → xylidide + acetaldehyde → further hydrolysis, hydroxylation Some metabolites have anti-arrhythmic effects CL dependent on liver function and blood flow
Elimination	$T_{1/2}$ = 100min Metabolites excreted urine
Pharmacodynamic	

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Mechanism action	1. Unionised portion diffusion across axonal membrane into axoplasm 2. In axoplasm, protonated to ionised form 3. Binds to fast Na channels in open, inactive state with frequency dependent blockade → blocks AP propagation.
Uses	Topical anaesthesia Peripheral nerve block IV regional block (Bier's block) Regional nerve block – usually only for test dose (short-acting) Anti-arrhythmic (VF/VT)
Dose	Max 3mg/kg 7mg/kg with 0.5% adrenaline
Local effects	Vasodilation at low dose, constriction at high dose Allergy rare Neurotoxicity: Transient radicular irritation – neural inflammatory reaction 24 hours after block Cauda equine syndrome: lumbosacral plexus injury with bilateral sensory anaesthesia, bowel/bladder dysfunction, paraplegia ASA syndrome: thrombosis of ASA → motor and ST deficit
Systemic effects	CNS: above 4µg/mL – excitatory circumoral tingling, numb tongue, agitation, confusion (block inhibitory neurons) → inhibitory sedation, LOC, coma, death CVS: above 20µg/mL – ↑ PR, QRS, RP times, ↓ SVR → myocardial depression → CV collapse
Allergy	Rare
Physiological states	Pregnancy – progesterone → ↓ α_1 acid glycoprotein → ↑ free drug → ↑ potency Unionised, protein free drug can cross placenta → ion trapping if acidosis in foetus
Drug interactions	1. ↓ MAC inhaled anaesthetics (halothane, nitrous) 2. ↑ duration NMBDs

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ANAESTHESIA

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Pharm-03A3 Explain how lignocaine prevents the conduction of a nerve action potential.

1. Lignocaine is an amide local anaesthetic drug used for the conduction blockade of nerve fibres. It is used commonly in anaesthetic for topical, regional, subcutaneous and epidural nerve blockade. The mechanism of action can be divided into:
    a. Diffusion to site of action
    b. Binding to fast Na channels
    c. Nature of AP blockade

2. Diffusion to site of action is necessary to for lignocaine to exert its therapeutic effect. The factors affecting diffusion are summarised by Fick's law:

$$\textbf{Diffusion} = \frac{\textbf{Sol x A x } \Delta\textbf{P}}{\sqrt{\textbf{MW}}\textbf{xT}}$$

    a. Type of nerve block affect the area, thickness –
        i. Topical - diffusion of drug to epidermal / submucosal pain fibres → used to block applied surface areas (usually small)
        ii. Peripheral nerve block – diffusion of drug to specific afferent nerve → used to block sensory nerve areas (medium sized area)
        iii. IV Bier's block – application of drug intravenously distal to tourniquet compression → diffusion of drug to nerve supplied by major vein → used to block limbs
        iv. Regional nerve blockade → diffusion of drug to a specific nerve root → used to block nerve root dermatomes (large areas)
        v. Spinal/epidural blockade → diffusion to spinal cord ascending sensory pathways → used to block largest areas
    b. Solubility - lignocaine weak base, pKa 7.9 which exists in equilibrium:
        Lignocaine + H^+ ⇔ Lignocaine-H^+
        The unionised form is more lipid soluble, and responsible for diffusion into nerve area.
        i. pKa – pH relationship:
            1. at body pH 7.4, 25% lignocaine unionised
            2. additive: bicarbonate additive will ↑pH solution → ↑ unionised portion → ↑ lipid solubility
            3. body pH: areas of inflammation are acidic → ↓ pH → ↓ solubility lignocaine → ↓ effect
    c. Distribution: lignocaine is most effective when drug remains in its site of action (local area) and NOT absorbed systemically
        i. Blood flow:
            1. ↑ blood flow ↑ systemic absorption → ↓ amount diffusion into local site.
        ii. Vasoactive properties
            1. Lignocaine has intrinsic vasodilator properties at low doses → ↓ local diffusion
            2. Addition of adrenaline offsets this effect

3. Blockade of fast Na channels
    a. Normal AP propagation:
        i. membrane Na channels are voltage gated, transmembrane protein channels. They exist in 3 states: closed, open-active, open-inactive.
        ii. Action potential transmission depends on voltage-stimulated opening of Na channels (open-active) to generate Na influx and membrane DP. The channel

becomes open-inactive before changing to its resting closed state. During open-inactive state → cannot be depolarised again.

b. Channel blockade:
    i. Once lignocaine enters the cytoplasm (with ↓pH), it becomes protonated. This protonated (ionised) form has ↑ affinity for Na channel.
    ii. Binds to Na-channels in open-inactive state, thereby preventing further activity → inhibits further AP transmission
    iii. Therefore, since open-inactivated states a re required for action, lignocaine acts by *frequency dependent blockade* → firing afferents are blocked first.

4. Nature of blockade: describes how nerve nature and environment affects amount required.
   Cm = minimal conc lignocaine required to achieve blockade
    a. Size – smaller, shorter nerves blocked before larger
    b. Position – central nerve fibres ↑Cm, ↓speed onset, but ↑ duration action
    c. Fibres type – C fibres (pain, post-ganglionic SNS) < B fibres < Aδ fibres (fast pain) < Aα (motor)
    d. Myelination – myelinated fibres blocked before non-myelinated
    e. Location – spinal blocked before epidural (↓ diffusion distance)

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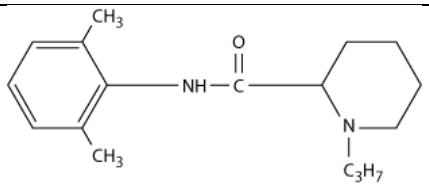
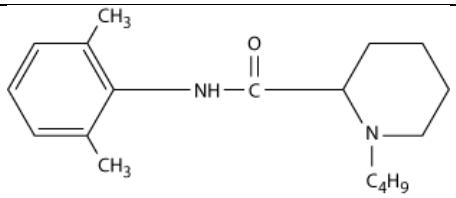
Pharm-04B2/98B15/94 Write a brief description of the pharmacology of ropivacaine and explain why it may be considered a safer agent than bupivacaine.

1. Ropivacaine and bupivacaine are long-acting amide local anaesthetics used to block conduction of afferent nociceptive nerve fibres.

	Ropivacaine	**Bupivacaine**
Pharmaceutical		
Structure		
Group	Amide with propyl side-chain	Amide with butyl side-chain
Isomers	Prepared as pure S-enantiomer R enantiomer ↑ toxicity, ↓ potency	Racemic mixture 1:1 of R and S enantiomers R enantiomer → ↑ toxicity, ↑ motor blockade Levobupivacaine: pure S-enantiomer
Structure activity	↑ propyl side chain length on hydrophilic end → ↑ lipid solubility Amide bond → liver metabolism	↑butyl side chain length on hydrophilic end → ↑ lipid solubility Amide bond → liver metabolism
Formulation	Colourless solution – 0.2%, 0.75%, 0.1%	Colourless solution – 0.25%, 0.5% Heavy solution – 0.5% with 80mg/mL glucose for epidural
O:W Lipid solubility	2.9 Lipid solubility > lignocaine, < bupivacaine	28 10x more lipid soluble than lignocaine
pKa	8.1 Weak base	8.1 Weak base
%unionised	15%	15%
Protein binding	94% α_1 acid glycoprotein	95% bound α_1 acid glycoprotein
Pharmacokinetics		
Absorption	Low F → high 1st pass metabolism Site-dependent: intrapleural > intercostals > caudal > epidural > brachial > SC Vasoconstriction (adrenaline) ↓ systemic absorption	
Distribution	VD 0.5L/kg 94% protein bound Offset depends on distribution	VD 1L/kg 95% protein bound Offset depends on distribution
Metabolism	Liver CL = 0.8L/min Hydroxylation (CYP 450) → 3OH ropivacaine → partial activity	Liver CL = 0.5 L/min Dealkylation → pipcolyloxylidine → no activity
Elimination	Metabolites excreted urine $T_{1/2}$ = 120min	Metabolites excreted urine, 16% unchanged $T_{1/2}$ = 160min
Pharmacodynamics		
Mechanism	1. Diffusion unionised drug into axoplasm to become ionised (Fick's law diffusion) 2. Binding to Na channel open-inactive 3. Rate-dependent block APs Ropivacaine has slower onset, less dense, shorter duration than bupivacaine (Onset 10-20min, duration 5-16 hours)	
Use	1. SC infiltration 2. Regional nerve block 3. Epidural	

	4. Intrathecal Neither drug is suitable for IV Biers block due to risk of CV collapse	
Dose	Max 2mg/kg	Max 2mg/kg
Local toxicity	Vasoconstrictor properties (most of LAs) at low doses, so adrenaline not needed	Vasodilation at low doses < lignocaine, > ropivacaine → adrenaline added.
Systemic toxicity	Generally toxicity < bupivacaine, > lignocaine CNS: dose dependent excitatory effects (circumoral tingling, paraesthesia, twitching, confusion, seizures) → inhibitory (↓ LOC, coma, respiratory depression, death) CVS: type I anti-arrhythmic properties (↑PR, QRS intervals and RPs), ↓ SVR, cardiac depression / collapse Bupivacaine is more cardiotoxic – it binds to cardiac Na channels, and dissociates less easily. CC:CNS = 5 ropivacaine, 3 bupivacaine	
Allergy	Rare	
Pregnancy	94% protein bound → only small unbound drug can cross placental Fetal acidosis → ion trapping	95% protein bound → only small unbound drug can cross placental Fetal acidosis → ion trapping
Drug interactions	↓ MAC volatile agents ↑ duration NMBDs	

2. Reasons for ↑ safety of ropivacaine:

Property	**Mechanism**	**Ropivacaine**	**Bupivacaine**
Isomers	The R enantiomer have ↑ lipid solubility and ↑ toxicity	Ropivacaine is a pure S-enantiomer	Bupivacaine is a racemic 1:1 mixture of R and S enantiomers
Lipid solubility	↑ lipid solubility → ↑ uptake by CNS/CVS → ↑ toxicity	Shorter side-chain (propyl), lower O:W = 2.9 → ↓ solubility	Longer side-chain (butyl), higher O:W = 28 → ↑ solubility
Vasoactivity	local vasodilation → ↑ blood flow → ↑ systemic absorption → ↑ distribution to CNS and CVS	More vasoconstriction at low doses	More vasodilation at low doses (used with adrenaline)
Clearance	↑ systemic clearance → ↓ plasma conc → ↓ toxicity	CL = 0.8L/min hepatic $T_{1/2}$ = 120min	CL = 0.5L min hepatic $T_{1/2}$ = 160min
Cardiac receptor action	↑ affinity cardiac Na channels → ↑ cardiotoxicity	Faster dissociation from cardiac Na channels	↓ dissociation from cardiac Na channels

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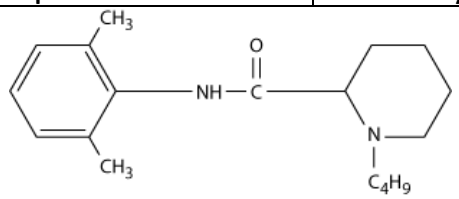
Pharm-97A13/92/91 List the physico-chemical characteristics of bupivacaine. Explain how they influence its pharmaco-dynamic effects at the site of administration and its cardiovascular toxicity.

1. Relationship between physiochemical properties and Pharmacodynamic effect

Property	Bupivacaine	Pharmacodynamic effect
Structure		
Group	Amide	Amide local anaesthetics are metabolised in the liver (unlike ester, by pseudocholinesterase in plasma / tissues) and have longer duration of action Unlike esters, metabolites are not PABA analogues → ↓ likelihood hypersensitivity
Structure activity	Butyl group on amine end	↑ side-chain length → ↑ lipid solubility → ↑ potency, speed of onset and toxicity
Isomers	1:1 R and S enantiomers	R enantiomer more lipid soluble, toxic compared to S isomer Levobupivacaine is a pure S-isomer → better toxicity profile
Formulation	0.25-0.5% solution 0.5% solution heavy glucose 80mg/mL 0.05% adrenaline	↑ concentration → ↑ potency → ↑ speed onset / duration action Adrenaline → vasoconstrict → ↓ systemic absorption → ↑ duration
pKa	8.1	Weak base: bupivacaine + H^+ ⇔ bupivacaine-H^+ At body pH 7.4, 15% unionised → not much drug diffuses → medium onset action 10-20min (> lignocaine, 3-5min 25% unionised) Tissue pH: inflammation ↓pH → ↓ penetration Bicarbonate: additive to ↑ pH → ↑ solubility → ↑ onset
Protein binding	95% α_1 acid GP	Highly protein bound → protein complexes held at target site (do not diffuse as easily) → long duration anaesthetic (5-16 hours)
O:W coefficient	28	Most lipid soluble local anaesthetic (10 x lignocaine) Accounts for long duration action, high systemic toxicity Prenancy: protein displacement from progesterone → ↑ free drug
Vasoactivity	Vasodilates at low dose	Vasodilation (< lignocaine, > ropivacaine) → ↑ systemic absorption → ↑ toxicity, ↓ duration Therefore, adrenaline effective

2. Cardiac toxicity
    a. Mechanism:
        i. Absorption into systemic circulation depends on –
            1. Local blood flow
            2. Site action
        ii. Distribution into Cardiac tissue
            1. Lipid solubility
        iii. Drug-receptor interaction
            1. Bupivacaine has high affinity for cardiac Na channels, to which it binds and blocks in the inactive-open state.

2. Rate of dissociation very low compared to other amides → persistent cardiac depression of automaticity.
3. Rate dependent blockage exacerbated by associated tachycardia

b. Clinical manifestations:
   i. ↓ contractility, ↓ SVR, ↑ HR
   ii. ↑ PR, QRS interval, ↑ refractory period
   iii. Re-entrant arrhythmias, VT/VF
c. CC:CNS = 3

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Pharm-08A6 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?

1. Cocaine is an ester of benzoic acid and used as a topical local anaesthetic and vasoconstrictor. Lignocaine is an amide local anaesthetic and a type 1b anti-arrhythmic. Adrenaline is a catecholamine, commonly used with local anaesthetics due to its potent vasoconstrictor properties.

2. Toxic doses: the toxicities of cocaine, lignocaine and adrenaline are additive and therefore maximum doses should be halved.

Drug	**Toxic level (mg/kg)**	**Case dose amount**	**Case dose safety**
Cocaine	3	5% = 50mg/mL	210mg/50 = 4.2mLs/2 = 2.1mls
Lignocaine	3 with adrenaline 7 no adrenaline	2% = 20mg/mL	490mg/20 = 24.5mls/2 = 12.25mls
Adrenaline		1:100000 = 10mcg/mL	12.25mLs lignocaine +adrenaline = 122.5mcg → Significant dose

3. Cocaine toxicity:
    a. Mechanism of action:
        i. Ester local anaesthesia – blocks fast Na-channels in an activity dependent manner → prevents depolarisation and propagation of AP
        ii. Blocks reuptake monoamines – blocks transport reuptake of NA, monoamine, dopamine → ↑levels at CNS synapses
        iii. MAO inhibitor → ↑ levels of monoamines
    b. Toxicity:
        i. CNS – local anaesthetic toxicity with initial excitation (paraesthesia, euphoria, seizures) followed by depression (drowsiness, disorientation, coma)
        ii. CVS:
            1. LA toxicity – myocardial depression, ↑QT intervals, ventricular arrhythmias
            2. Monoamine toxicity – coronary vasospasm
    c. Drug interactions:
        i. Lignocaine – potentiates CNS and CVS toxicity
        ii. Adrenaline – potentiates CVS vasospasm and arrhythmogenicity.