B3 - Local anaesthetic drugs

Classification

Ester

- cocaine
- procaine
- amethocaine
- cholroprocaine

Amide

- lignocaine - ethyl chains (C2H5)
- prilocaine
- bupivacaine - butyl tail (C4H9)
- levobupivacaine
- ropivacaine - propyl tail (C3H7)
- mepivacaine - methyl tail (CH3)
- etidocaine

(a) To describe the structure-activity relationship of LA drugs

Aromatic ring + Ester or Amide Bond + Basic amine side chain

See diagram of Lignocaine for example

- weak bases
- pKa 8 to 9 thus, mainly ionized @ physiological pH
- LA with pKa closer to physiological pH, as weak bases, will have more rapid onsets (it is the non-ionised form of the drug that most easily penetrates the neuronal membrane + myelin sheath)
- however, once LA has entered, it's the ionised form that interacts with the Na+ channel to prevent its activation.

Aromatic ring

- lipophilic (essential for anaesthetic activity)
- to increase lipophilicity -> increase length of alkyl substituents

Bond

Ester (-C-O-O-) - inactivated by non-specific esterases (liver/tissues)

- cocaine

- procaine
- amethocaine
- cholroprocaine

- cause more allergic reactions
- less stable
- heating neutralises
- higher pKa's (penetrate tissue less readily)

Amide (-NHOC-) - more stable -> longer plasma t1/2

- lignocaine - ethyl chains (C2H5)
- prilocaine
- bupivacaine - butyl tail (C4H9)
- levobupivacaine
- ropivacaine - propyl tail (C3H7)
- mepivacaine - methyl tail (CH3)
- etidocaine

- amides have replaced esters as LAs because they do not cause as many allergic reactions.

Amine side chain

- hydrophilic
- to decrease hydrophilicity -> increase length of alkyl substituents

Pipecoloxylidide LA's = chiral drugs that are produced in racemic mixtures

- mepivacaine
- bupivacaine
- ropivacaine

Non-pipecoloxylidide LA's = pure S enantiomers - less CNS & CVS toxicity

- ropivacaine
- levobupivacaine

(b) To describe the mechanisms of action of LA drugs.

- produce a conduction blockade of nerve impulses by inhibiting passage of Na+ ions through ion-selective Na+ channels in nerve membrane.
- block the initiation & propagation of action potentials by preventing the voltage-dependent increase in Na+ conductance.

See diagram - explaining change in ion conductances in an action potential.

- LA decreases the permeability of Na+ channel -> slows the rate of depolarisation -> threshold for action potential not reached -> action potential not propagated.
- block Na+ channel by physically plugging the transmembrane pore

See diagram - Na+ channel diagram (on computer)

- LA do not alter the RMP of a cell membrane.
- they diffuse unionised through the site of deposition, through:

(1) nerve sheath (epineurium)
(2) perineuronal tissue (perineurium)
(3) neuronal membrane (endoneurium)
(4) axoplasm (myelin sheath & nerve fibre)

- bind to the alpha subunit
- preventing conformational changes from inactivated/closed state that allows opening of the gate between domain III & IV.

- Na+ channels in the resting, closed state have a much lower affinity for LA

- during onset & recovery, repetive stimulation produces additional use-dependent binding to Na+ channels.
- LA molecules gain access when the channels are in open or inactivated state.

Progressive change in function:

(1) increase threshold for excitation
(2) slowing of impulse conduction
(3) reduced rate of rise of action potential
(4) abolished action potential

Pain transmitting fibers:

- Myelinated A-delta
- Non-myelinated C fibres

-> both fibres are blocked with simialr concentrations of LA.

Cm = minimum concentration of LA needed for concentration blockade (analagous to MAC)

Increased Cm required for:

- large fibres
- motor fibres

Decreased Cm required for:

- sensory fibres
- small fibres
- increased tissue pH
- high frequency nerve stimulation

(c) To describe the formulations of LA and their clinical importance.

Surface Anaesthesia

EMLA

- eutectic mixture = mixture of constituents @ a ratio that producers the lowest temperature melting point.

- non-crystaline mixture
- white cream
- 2.5% lignocaine & 2.5% prilocaine in oil:H2O emulsion
- works by diffusion through intact skin to block neuronal transmission from dermal receptors.

Uses:
- used for venepuncture
- SSG
- arterial cannulation
- LP
- myringotomy

Local reactions:
- pallor
- erythema
- puritis
- rash

- topical under occulsive dressing
- anaesthesia for 1-5hrs
- causes temporary blanching & oedema of skin
- detectable methaemoglobinaemia

Cocaine

- popular because it produces localized vasoconstriction -> decreases blood loss

Lignocaine

- nebulised to produce upper & lower respiratory tract anaesthesia.

Uses:

- fibre optic laryngoscopy
- bronchoscopy
- treatment of intractable coughing

- well absorbed into the systemic circulation via mucous membranes.
- bioavailabilty = close to 100%

Local Infiltration Anaesthesia

- extravascular placement of LA

LA types:
- lignocaine 1-2%
- ropivacaine 0.25%
- bupivacaine 0.25%

- duration of infiltration anaesthesia can be doubled by adding 1:200,000 adrenalin.
- DO NOT inject into tissues supplied by end-arteries -> vasoconstriction -> ischaemia.

IV Regional Anaesthesia

- Bier Block
- IV injection of LA solution into an extremity isolated from the rest of the systemic circulation by torniquet.
- produces rapid onset of anaesthesia & sk muscle relaxation.
- duration dependent on when torniquet is let down.

LAs:
- lignocaine
- prilocaine
- mepivacaine
- ropivacaine

Nerve block Anaesthesia

- injection of LA into tissues surrounding individual peripheral nerves or nerve plexuses (ie. brachial plexus).

- LA diffuses from the outside -> inside (core) along a concentration gradient.
- proximal structures anaesthetised first then distal.
- recovery takes place in opposite direction (distal first and then proximal)
- nerve fibres on the outside are exposed to the extraneural fluid and therefore lose LA.
- skeletal muscle paralysis may preceed the onset of sensory anaesthesia -> if motor fibres involved in a mixed peripheral nerve.

Onset:
- rapidity of sensory anaesthesia are proportional to the pK of drug.
- pK determines the amount of active nonionized form at the pH of the tissue.

Duration of block:
- dose of LA
- lipid solubility
- degree of protein binding
- use of epinephrine

Spinal anaesthesia

- injection of LA into the lumbar subarachnoid space.
- LA acts on (1) superficial layers of spinal cord, (2) preganglionic fibres as they leave the spinal cord in the anterior rami.

- the level of sympathetic nervous denervation **extends 2 spinal segments cephalad** from sensory level.
- the level of motor block **extends 2 spinal segments below** sensory level.

Dosage of LA depends on:

(1) height of patient - determines volume of subarachnoid space.
(2) segmental level of anaesthesia desired.
(3) duration of anaesthesia desired.

- dose is more important than volume or concentration of drug.

LAs:
- tetracaine
- lignocaine
- bupivacaine
- ropivacaine
- levobupivacaine

- the specific gravity of a LA solution injected into the lumbar CSF is important in determining spread of drugs.
- addition of glucose to solutions increases the specific gravity -> makes the solution hyperbaric.
- addtion of distilled H2O lowers the sg -> makes solution hypobaric.

Density = weight in grams of 1mL of liquid (related to temp - measured @ 37C)
Specific gravity = density of a solution : density of water (0.9934)
Baricity = density of a spinal anaesthetic : density of CSF (1.0003)

>1 hyperbaric
<1 hypobaric

Available in NZ\Australia

- Bupivicaine 0.5% in H2O - barcity = 0.9990
- Bupivicaine 0.5% in H2O in 8% glucose = 1.0207

Epidural anaesthesia

- produce anaesthesia via two presumed mechanisms:

(1) LA diffuse across dura to act on nerve roots & spinal cord.
(2) LA diffuses into paravertebral area through the intervertebral foramina -> multiple paravertebral nerve blocks.

- there is about a 15 to 30 min delay until onset.

Agents:
- lignocaine (readily diffuses through tissues)
- bupivacaine
- levobupivacaine (0.5-0.75%)
- ropivacaine (0.5-0.75%)

- addtion of 1:200,000 epinephrine doesn't seem to offer any advantage.

(d) To describe the pharmacokinetics of LAs and potential alterations with physiological & pathological disturbance.

Absorption

- dependent on Ficks Law of Diffusion =

$$-DA.\frac{\text{change in c}}{dc}$$

Site

A = area over which absorption takes place.
dc = diffusion distance

Dose

Change in c = concentration gradient

Specific properties of agent

D = specific properties of agent

- vasoconstrictor/dilator
- lipid solubility
- degree of ionization (pKa = the pH at which the ionized and non-ionized portions of LA are equal)
- plasma protein binding (effects duration of action)
- molecular weight

- unique factors

Note:

- 1 pH unit from the pKa -> change from 75% in degree of ionization.
- 2 pH units from the pKa -> change from 90% in degree of ionization.

Distribution

- the lungs are capable of extracting LA sucha s lignocaine, bupivacaine & prilocaine from circulation.

Metabolism

Ester
-> rapidly hydrolysed by plasmacholinesterase.
- prime metabolite = para-aminobenzoic acid

Amides
-> enzymatic gradation in liver
- initally conversion of amide base -> aminocarboxylic acid + cyclic aniline derivative
- then aminocarboxylic acid -> hydroxylated
- and aniline moiety -> N-dealkylated

- ie. lignocaine -> oxidative dealkylation to monoethylglycinexylidide -> hydrolysis to xylide.

Elimination

- clearance and t1/2's for amide LA these represent hepatic metabolism, because renal excretion of unchanged drug is minimal.

- poor water solubility of LA usually limits renal excretion of unchanged drug < 5%

Alterations in physiological & pathological circumstances

- increase in K+ -> increases inactive channels -> increase effect of LA

- pregnancy -> increase effect of LA by decreasing protein binding

- LA = weak bases with pKa's of higher than physiological pH -> if injected into areas of high acidity (infections), low pH -> increases ionized fraction -> less absorption.

- decreased liver function or blood flow -> decreased metabolism of amide LA's

- addition of epinephrine -> decreases systemic absorption -> increases duration of block, decreases blood loss, less systemic absorption (safer)

(e) To describe the pharmacodynamics of the LAs with particular reference to the neuronal, central nervous system & cardiovascular effects.

Physiological effects

CVS

- hypotension (33%)
- risk factors: sensory level above T5, SBP < 120mmHg.

- bradycardia (13%)
- risk factors: sensory level above T5, HR < 60/min, prolonged P-R interval & use of beta-blockers.

- sympathetic block -> arteriolar dialatation -> decrease in SVR by <15%.

- sympathetic block -> venous dialatation -> increase in venous capacitance -> decrease VR -> decrease Q -> MAP

- suppression of venticular dysrrhythmias & increase in the debrillation threshold.

RESP

- apnoea occurs with excessive level of spinal anaesthesia.
- secondary to ischaemic paralysis of the medullary ventilatory centres from profound hypotension & decrease in CBF.
- bronchodilation -> IV low dose -> decrease bronchial reactivity.

CNS

- analgesia -> can be administered for post-op pain in low dose (IV)
- suppression of generalized tonic-clonic fits in low dose.

Metabolic

Anti-inflammatory Effects:

- LA modulate inflammatory responses and may be useful in mitigating perioperative inflammatory injury.
- Over reactive inflammatory responses involved in: post-op pain, ARDS, SIRS & multi-organ failure.
- beneficial effects attributed to epidural anaesthesia - pain relief, decreased DVT -> attributed to anti-inflammatory effects of LA.
- LA inhibit platelet-activating factor.
- LA inhibit G-proteins: these are involved in many mediators - thromboxane, thrombin, platelet activating factor, & interleukins.
- LA inhibit neutrophil accumulation & impair free radical & mediator release.

(f) To explain the factors that determine the clinical effects of LA.

Summary

(1) Site
(2) Dose
(3) Intrinsic properties of drug
(4) Patient factors

Speed of onset of LA's relate to factors affecting the drugs passive diffusion through biological membranes = **Ficks Law of Diffusion =**

-DA.change in c/dc

A = area over which absorption takes place.
dc = diffusion distance
Change in c = concentration gradient
D = specific properties of agent

(1) Site

- influences dc

(a) peripheral nerves

- fibre arrangement -> more distal distribution = core, more proximal parts = mantle. Thus loss of sensation goes from proximal to distal.
- fibre diameter -> increased concentration of LA needed for larger fibres
- fiber firing frequency -> LA more effective on faster firing fibres.
- disposition of LA near nerve -> if site is more vascular -> more rapid uptake -> shorter duration.

(b) epidural factors

3 mechanisms: - slow diffusion = 15 to 30 delay in onset.

(1) LA diffuses across the dura to act on nerve roots and spinal cord.
(2) LA also diffuses into paravertebral area through intervertebral foramina -> multiple paravertebral blocks
(3) venous systemic uptake

(b) spinal factors

- injection of LA into lumbar subarachnoid space

Mechanisms:

(1) act on superficial layers of spinal cord
(2) preganglionic fibres as they leave the cord in anterior rami.

- Zones of differential anaesthesia derived.
- Sympathetic block 2 levels above sensory level.
- Motor block 2 levels below sensory level.

- doses vary with height of patient, segmental level of anaesthesia desired & duration of anaesthesia required.

(2) Dose

- membrane thickness influences dc

(3) Intrinsic Drug Properties

= D

(a) intrinsic vascular activity

- vasoconstrictors - cocaine, S-ropivacaine
- vasodialators - lignocaine > mepivacaine

(b) lipid solubility & pKa

- lipid soluble agents more easily penetrate myelin sheath and reach the sit of action -> are more potent.
- drugs with a rapid onset have pKas closer to physiological pH -> greater proportion of unionised membrane-penetrable form.
- addition of HCO3 is theoretically meant to increase onset -> but there is not much clinical evidence.

(c) protein binding

- bupivacaine = 95%
- ropivacaine = 95%
- lignocaine = 70%
- prilocaine = 55%
- procaine = 6%

- highly protein bound -> longer duration of action.
- LA are basic drugs so bind to alpha 1 acid glycoprotein.

(d) increased concentration

- may increase absorption by saturating local binding sites or by vasodilation

(e) molecular weight

- prilocaine lowest (220)
- bupivacaine highest (228)
- ? related to diffusion of LA into Na+ channel

(4) Patient factors

- **increased K+** -> increases RMP -> increases number of inactive channels -> increased effect of LA

- acidity of tissues -> decreases pH -> increases the amount of ionised LA -> delays absorption

- young age -> decreased metabolism -> greater faction unchanged, decreased levels of alpha 1 acid glycoprotein -> increased free fraction of drug.

- old age -> renal impairment, increased hepatic oxidation & N-dealkylation elimination of bupivacaine & lignocaine.

- hepatic impairment -> impaired metabolic capacity, low hepatic blood flow -> increased duration of action.

- drug interaction - cimetidine -> prolongs elimination half life of lignocaine.

- pregnancy

- more rapid onset of blockage c/o changes in protein binding.
- ester LA are rapidly hydrolysed -> not available to cross the placental barrier in significant amounts.

Maternal

- increased tissue sensitivity to LAs due to increased progesterone.
- engorged epidural blood vessels -> higher risk of intravascular injections.
- reduced plasma protein binding

Fetal

- LA will enter fetus
- placental transfer effected by - maternal free drug concentration, degree of ionisation, metabolis, pH of fetus (fetus-ion trapping when fetus acidotic)

(g) To compare the pharmacology of LAs with particular reference to lignocaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine, cocaine & procaine.

Lignocaine (fast in, fast out)

Chemical - amide derivative of diethylaminioacetic acid

Uses:

(1) reversible neural blockade
(2) treatment of ventricular dysrrhytmias (class Ib antiarrhythmic)

Structure - see diagram

Physiochemical:

- pKa 7.7 (fast onset)
- 65% protein bound (moderate duration)
- preservative free
- 35% nonionized at pH of 7.4

Presentation:

- injection - clear, colourless solution
- gel
- ointment (5%)
- spray (10%)
- aqueous solution (4%)
- cream suppositories +/- hydrocortisone

Infiltration - 5mg/mL (0.5%), 10mg/mL (1%)
Peripheral nerve blocks - 10 (1%), 15 (1.5%), 20mg/mL (2%) with or without adrenaline.
Epidural - 10, 15 & 20mg/mL solutions
Spinal - 50mg/mL solution
Topical - 2% jelly, 2.5% & 5% ointment.

Route

- infiltration
- topical
- IV
- spinal
- epidural

Dose

- max IV dose = 300mg
- max dose 3mg/kg
- max dose with adrenaline 7mg/kg
- dose for ventricular arrhythmias = 1 mg/kg bolus over 2min -> infusion @ 4mg/kg for first 60min, then 2mg/kg for next hour, then 1mg/kg after that.

PK

Absorption

- related to site, dose and presence of vasoconstrictors.
- bioavailability PO = 30% - high first pass metabolism.

Distribution

- Vd = 1L/kg
- 64% protein bound (to alpha-1 acid glycoprotein)

Metabolism

- hepatic (70%)
- N-dealkylation to monoethylglycinexylidide -> hydrolysis to xylidide

Elimination

- <10% excreted in urine unchanged.
- Cl = 10mL/min/kg
- Elimination t1/5 = 100 min
- reduced in cardiac & hepatic failure.

PD

Main action - see (b)

- acts within 10min
- lasts within 200-400min

Mode of action - see (b)

CVS

- CC/CNS 7:1 = 7 times as much drug dose required to produce CVS collapse compared to convulsions.
- depression of rate of cardiac AP
- hypotension from smooth muscle relaxation & myocardial depression.
- prolongation of P-R & QRS.

RESP

- bronchodilation
- respiratory depression @ toxic doses.

CNS

- reversible neural blockade -> biphasic effect
(1) excitation - lightheadness, dizziness, visual & auditory disturbances, fitting.
(2) blockade of inhibitory pathways in cortex - drowsiness, disorientation & coma

GI - depress contraction of the intact bowel.

Metabolic - anticholinergic & antihistaminergic activity.

Prilocaine

Chemical - seconardy amine which is am amide derivative of toluidine (prilocaine hydrochloride)

Uses - LA

Preparation

- 5,10, 20 & 40 mg/mL solutions
- 3% solution with 0.03 IU felypressin/mL

Physiochemical

- pKa 7.7 (fast onset)
- heptane:buffer partition co-efficient = 1

Routes

- infiltration
- epidural
- topically (EMLA)
- IV (in Beirs Block)

Dose

- toxic dose = 6mg/kg (with felypressin 8mg/kg)

PK

Absorption

- related to site, dose, presence of vasoconstrictors

Distrbution

- 55% protein bound (moderate duration of action)
- bound by alpha-1-acid glycoprotein.

Metabolism

- hepatic (some in lung & kidney)
- to O-toludine -> 4 & 6 hydroxytoludine
- O-toludine may lead to methaemoglobinaemia (patient cyanotic with decrease O2 carrying capacity) -> responds to methylene blue (1-2mg/kg)

Elimination

- <1% unchanged in urine
- inactive metabolites in urine

PD

Main action - LA

Mode of action - see (b)

- duration of 1.5 x longer than lignocaine.

CVS

- in low dose -> mild increase in BP
- in toxicity -> decreased SVR & contractility -> hypotension -> cardiovascular collapse.

RESP

- low dose -> bronchodilation
- toxic dose -> respiratory depression

CNS

- seizures @ 7mcg/mL (same as lignocaine)
- same as lignocaine

GI - depress contraction in bowel

Bupivacaine (fast in, slow out)

Chemical - structural homologue of mepivacaine (pipecoloxylidide amide)

Uses - LA

Structure - see diagram

Preparation - out of patent so CHEAP!

Solutions

- 0.25, 0.5% +/- 1:200,000 epinephrine
- 0.5% 'heavy' contains 80mg/mL of glucose (sg 1.1)

Epidural solutions

- 100mL 0.125%
- 100mL 0.125% with fentanyl 5mcg/mL

Physiochemical

- pKa 8.1 (moderate onset)
- heptane:buffer partition coefficient = 30 (very lipid soluble)

Routes

- topical
- infiltration
- intrathecally
- epidurally

Dose

- toxic dose = 2mg/kg (with or without vasoconstrictor)

PK

Absorption

- related to site & dose
- epinephrine doesn't affect systemic absorption as highly lipid soluble & drug has an intrinsic vasodilatory effect.

Distribution

- 95% protein bound (long duration)
- Vd = 1 L/kg

Metabolism

- hepatic

- by N-dealkylation -> pipecoloxylidine

Elimination

- 5% excreted as pipecolyloxylidine in urine.
- 16% unchanged
- Cl = 7 mL/kg/min
- Elimination post IV dose T 1/2 = 30min

PD

Main action - LA

Mode of action - see (b)

- 4 x as potent as lignocaine
- acts within 15min
- lasts 6-16hrs

CVS

- markedly cardiotoxic -> binds to myocardial proteins.
- CC/CNS ratio 4:1
- toxicity -> decreases SVR & myocardial contractility

RESP - see previously
CNS - see previously

Note - significantly increases the duration of all types of muscle relaxants.

Levobupivacaine

Chemical - S(-) enantiomer of bupivacaine

Uses - LA

Structure

Preparation

Physiochemical

- pKa 8.1

Route

- infiltration
- epidural
- PNB
- spinal

Dose -

PK

Absorption - dependent on site, dose & vasoconstrictor

Distribution

- > 97% protein bound
- fraction non-ionized @ pH 7.4 = 17%
- Vd = 60L

Metabolism

Elimination - t1/2 = 150min

PD

Main action - LA

Mode of action - see (b)

- onset slow
- lasts 4 to 8 hrs

? enantiomers bind to receptors or enzymes that are chiral amino acids with stereoselective properties.

- produce enhanced vasoconstriction & prolonged action
- also reduce the intensity & duration of motor block

CVS - less cardiotoxicity
CNS - less neurotoxicity

Ropivacaine

Chemical - aminoamide (pipecoloxylidide group) - S (-) enantiomer

Uses - LA

Presentation:

- 0.2, 0.75, 1% of ropivacaine HCl
- clear, colourless solution

Physiochemical:

- pKa 8.1
- heptane:buffer partition coefficient 2.9 (intermediate lipid solubility)

Routes

- topical
- infiltration
- epidural (alkalinisation increases duration of block)
- not for spinal use

Doses - toxic dose = 3mg/kg

PK

Absorption - see lignocaine

Distribution

- 94% protein bound
- Vd 60 L/kg

Metabolism

- hepatic
- CYP450 -> 2,6 pipecoloxylidide

Elimination

- Cl 1 L/min
- t1/2 = 11p min
- 1% excreted unchanged in urine
- 80% metabolites in urine

PD

Main action - LA

Mode of action - see (b)

- reduction in motor block
- only 60% as potent as bupivacaine

CVS - decreased risk of cardiotoxicity
CNS - seizures @ 5 mcg/mL

Cocaine

Chemical - ester of benzoic acid (naturally occuring alkaloid from the leaves of *Erythroxylon coca*)

Uses - LA + vasoconstriction & euphoria

Presentation

- 1-4% solution
- non-proprietary past of varying concentrations.

Physiochemical

Routes - topically

Dose - max dose = 3mg/kg

PK

Absorption

- bioavailability = 0.5% (intranasally)

Distribution

- protein binding 98%
- Vd 2 Lkg

Metabolism

- by plasma and (uniquely) liver cholinesterases -> H2O soluble metabolites

Elimination

- in urine
- 10% unchanged
- Cl 30 ml/kg/min
- t1/2 = 40min

PD

Main action - LA + vasoconstriction

- low dose -> decreased HR c/o increase in vagal tone.
- moderate dose -> increase in sympathetic tone = increase in HR & BP
- large dose -> euphoria, inhibition of myocardium -> VF.

Mode of action - see (b) + blocks reuptake of catecholamines at adrenergic nerve endings.

- blocks uptake of norad -> vasoconstriction, & dopamine -> CNS excitation

CVS - coronary vasospasm -> AMI, arrhythmias, tachycardia

RESP - increase RR -> depression

CNS

- biphasic response + hyperreflexia, mydriasis, increased ocular pressure
- seizures
- cerebral haemorrhage
- confusion & hallucinations

GI - hyperdynamic bowel sounds, N + V, pain.

Metabolic - inrcreased temp, motor activity & cutaneous vasoconstriction, DIC, rhabdo.

Procaine

Chemical = an ester LA

Uses - for every form of regional anaesthesia

Preparation

Physiochemical

- pKa = 9.0

Route - all routes

Dose - 20mg/kg

PK

Absorption

Distribution

- 6% protein bound (short duration)

Metabolism

- hydrolysed by plasma cholinesterase to para-aminobenzoic acid (PABA)

Elimination

- urinary excretion
- 50% excreted unchanged

PD

Main action - LA

Mode of action - see (b)

- low toxicity
- fast onset
- short duration

CVS

- vasodiation
- antiarrhythmic

CNS - see lignocaine

(h) To describe LA toxicity. To describe its prevention & management.

- 1 to 4 per 1000 patients
- bupivacaine most likely to be associated with this.

Systemic toxicity = excess plasma concentration of LA detemined by rate of drug enterance into systemic circulation relative to its redistribution to inactive tissue sites and clearance by metabolism.

- most common mechanism = accidental intravascular injection.

CNS effects:

Excitation phase

- numbness of tongue and circumoral tissue
- restlessness
- tinnitis
- vertigo
- shivering
- muscular twitching & tremors (initially involving muscles of face & distal parts of extremities)
- generalised convulsions

Depression phase

- generalised depression
- decreased LOC
- apnoea

- precise site for LA-induced seizures is not known.

CVS effects:

Initial - hypertension & tachycardia

Primary (effect on fast Na+ channels in heart) - negatvie iontropism, decreased CO2, mild-moderate hypotension

Secondary - peripheral vasodialatation, profound hypotension -> decreased Q

Terminal - sinus bradycardia, intracardiac conduction defects (prolonged PR & QRS complex), ventricular arrhythmias, cardiac arrest.

- mehanism = induced inhibition of cAMP

Treatment:

- ventilation
- high flow O2
- hyperventilation -> increased CO2, decreases convulsive threshold.
- IV midazolam or diazepam can suppress seizures
- legs up
- volume
- venopressors (ephedrine)
- atropine (bradycardia)

Prevention - aspirate & know your toxic doses!

Procaine - 20 mg/kg
Lignocaine - 3 (or 7 with epinephrine)
Prilocaine - 7
Bupivacaine - 2