B. 10 Local anaesthetic drugs

a. Describe the structure-activity relationships of local anaesthetic drugs.

composed of lipophilic end, chain and hydrophilic end
saturated groups at hydrophilic end increase lipid solubility, decrease water solubility, increase protein binding and potency, increase time to onset
pKₐ reduced by amide rather than ester linkage

Bupivacaine is N-\textbf{butyl}piperoclic xylidine. Mepivacaine is N-\textbf{methyl}~ and ropivacaine is (S) N-\textbf{propyl}~.
Benzocaine has no hydrophilic group and does not display frequency-dependent block.

b. Classify local anaesthetic drugs and list them under the appropriate group.

esters
- cocaine (from \textit{Erythroxylon coca})
- procaine
- nesacaine
- amethocaine
- benzocaine

amides
- prilocaine
- lignocaine
- etidocaine
- mepivacaine
- bupivacaine
- ropivacaine

other agents with LA activity
- barbiturates
- pethidine
- \textbeta{}-blockers
- phenol (6\% for neurolytic block)

c. Describe the mechanism of action of local anaesthetic drugs.

diffuse through cell membrane in basic form
ionized at intracellular pH
bind to voltage-gated Na⁺ channels in the open state
channel consists of \( \alpha \), \( \beta_1 \) and \( \beta_2 \) subunits
\( \alpha \) subunit has four homologous domains which form the channel
each domain has six subunits \( S_{1-6} \)
\( S_5 \) and \( S_6 \) form the m-gate
local anaesthetics bind to \( \alpha \) domain 4 \( S_6 \) in the open and inactivated states
cause stabilization of the inactive state
bind most rapidly with repetitive firing (frequency dependence)
lignocaine: fast dissociation
bupivacaine: slow dissociation
benzocaine: probably another mechanism
prevent channel opening
\( \uparrow \) threshold voltage, refractory period
\( \downarrow V_{\text{max}} \)
nerve
resistant to depolarization
\( B > C > A\delta - A\alpha \)
cardiac
wide QRS, long PR
\( \downarrow \) contractility

**d. Explain the principles of the pharmacokinetics of local anaesthetic drugs and apply this knowledge to use in clinical practice.**

<table>
<thead>
<tr>
<th></th>
<th>pK( _a )</th>
<th>bound</th>
<th>( t^{1/2} )</th>
<th>onset</th>
<th>duration</th>
<th>hepatic</th>
<th>( V_d )</th>
<th>lipid</th>
<th>sol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>lignocaine</td>
<td>7.9</td>
<td>70</td>
<td>1.6</td>
<td>fast</td>
<td>1-2</td>
<td>68%</td>
<td>1.3</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>bupivacaine</td>
<td>8.1</td>
<td>96</td>
<td>2.4</td>
<td>medium</td>
<td>2-6</td>
<td>37%</td>
<td>1.0</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>(S) ropivacaine</td>
<td>8.1</td>
<td>94</td>
<td>1.8</td>
<td>medium</td>
<td>4-6</td>
<td>40%</td>
<td>0.6</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>prilocaine</td>
<td>7.7</td>
<td>55</td>
<td>1.5</td>
<td>fast</td>
<td>1-2</td>
<td>high</td>
<td>2.7</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>procaine</td>
<td>8.9</td>
<td>3</td>
<td>1-10min</td>
<td>medium</td>
<td>.5-.75</td>
<td>low</td>
<td>0.6</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>cocaine</td>
<td>8.6</td>
<td>1-2</td>
<td>fast</td>
<td>topical</td>
<td>80%</td>
<td>low</td>
<td>0.6</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>etidocaine</td>
<td>7.7</td>
<td>94</td>
<td>2.4</td>
<td>fast</td>
<td>2-6</td>
<td>73%</td>
<td>1.9</td>
<td>141</td>
<td></td>
</tr>
</tbody>
</table>

**absorption**
all weak bases \( B + H^+ \leftrightarrow BH^+ \)
pKa falls with a rise in temperature (\( \uparrow \) unionized form)
distributed as acid solution of HCl salt
unionized species diffuses readily
\( \text{high pH} \rightarrow \text{rapid diffusion} \)

\( \text{hence addition of bicarbonate to solutions} \)
intracellular pH is lower
more ionized
ionized species is pharmacologically active
systemic absorption depends on site of administration
intravascular > intercostal > tracheal > caudal > epidural > plexus > local
speed of injection increases peak level slightly (epidural and plexus)

**distribution**
dependent on
route
lipid solubility (\( \downarrow \) onset time), water solubility
protein binding (\( \uparrow \) duration)
\( \text{pH: acidosis} \downarrow \text{diffusion} \)
temperature
perfusion
adrenaline reduces blood flow, intensifies motor block
ropivacaine is a vasoconstrictor

Local anaesthetics 2.B.10.2 James Mitchell (December 24, 2003)
susceptibility of nerve
   B > C > A
age
   children: rapid tracheal uptake, slow caudal uptake
spinal
   rapid uptake into spinal cord
   grey > white
dorsal root > ventral
   removal by partition into blood
   minor spread in CSF
   t'_of
   lignocaine 1 h
   bupivacaine 2 compartment 30% 1 h, 70% 6 h
epidural
   rapid diffusion into CSF (10-20 min)
   spread into spinal nerves by 30 min
   also spread into cord by diffusion into spinal arteries
   sequestered in epidural fat
   blood level peaks at 15-30 min
brachial plexus
   penetration of nerves from outside (distal, motor) to inside (proximal, sensory)
circulation
   distribution into lung tissue smooths arterial peak after IV injection
cross placenta readily
   rapid arterial injection can cause retrograde flow to cerebral circulation
bound to α, acid glycoprotein
   low level in pregnancy ↑ free fraction
   high level in
   renal failure (and low pH) ↓ action
   post op, trauma or AMI
cancer
   may result in “toxic” total plasma concentration from infusion
   post-op with unchanged free concentration due to increased
   binding
metabolism and excretion below

e. Explain the factors that determine the clinical effects of local anaesthetic
drugs.

f. Describe the metabolism of local anaesthetic drugs.

metabolism
   esters
   hydrolysed by plasma cholinesterase
   both in circulation and at site of action
   cocaine → benzoylecgonine → eegonine
   procaine → diethylamino ethanol + para-amino benzoic acid
   amides
   minimal metabolism at site of action
   hepatic metabolism by hydrolysis, dealkylation and hydroxylation
   perfusion limited except bupivacaine (↓ β-blockers, general anaesthesia)
   metabolism in immature in the neonate t'_of 2-3 times longer
   obesity prolongs t'_of due to slower redistribution
   bupivacaine < lignocaine < etidocaine < prilocaine
   lignocaine

Local anaesthetics 2.B.10.4 James Mitchell (December 24, 2003)
N-deethylation → glycine xylidide (LA)
amide hydrolysis → xylidine
3’ and 4’ hydroxylation are minor pathways
prilocaine
hydrolysis → o-toluidine + N-propylalanine in kidneys, liver and lung
→ methaemoglobin + 4- and 6-hydroxytoluidine
methaemoglobin is very slowly reduced in neonates
MetHb reduced to Hb with methylene blue 1-2 mg/kg
bupivacaine
poorly characterized metabolism
hydrolysis, 3’- and 4’- hydroxylation
ropivacaine
3’-hydroxylation, glucuronidation and renal excretion (40%)
minor N-dealkylation and 4’-hydroxylation
\( t^{1/2} \beta \) 1.8 h, E 0.4, clearance 6 ml/kg/min, \( V_d \) 0.6 ml/kg
\( t^{1/2} \) from epidural space 4.8 h
excretion
renal
filtration of free fraction and tubular secretion
1-6% excreted unchanged (increased in acidic urine)
hepatic metabolites are renally cleared
enteral
small amount of gastric secretion and intestinal reabsorption
coeXistent disease
cardiac failure
\( \downarrow V_d, \) clearance
hepatic failure
\( \uparrow V_d, \) \( t^{1/2} \beta, \downarrow \) clearance
renal failure, pulmonary disease
\( \downarrow \) clearance
drug interactions
general anaesthesia
\( \downarrow \) hepatic blood flow, \( \uparrow t^{1/2} \beta \)
adrenaline
\( \uparrow \) hepatic blood flow, \( \downarrow t^{1/2} \beta \)
\( \beta \)-blockers
propranolol → 40% reduction in pulmonary uptake of lignocaine
enzyme inducing and inhibiting agents
hepatic
cholinesterase (for esters)

g. Describe the management of overdoseage of local anaesthetic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Safe Dose (mg/kg)</th>
<th>Toxic Level (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lignocaine</td>
<td>5</td>
<td>6-8</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ropivacaine</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>prilocaine</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>procaine</td>
<td>5</td>
<td>7-10</td>
</tr>
</tbody>
</table>

“Safe dose” is for infiltration or regional block, not IV or spinal dose
40-50% higher dose for local infiltration with adrenaline
lower safe dose with \( \downarrow \) protein binding, \( \downarrow \) pH, \( \uparrow \) HR in neonates
cardiac:CNS toxicity ratio is a measure of safety
lignocaine 7:1
bupivacaine 3.7:1 (with slow offset of action)
central mechanism for some arrhythmias
L-bupivacaine is less toxic

lignocaine

<table>
<thead>
<tr>
<th>Level (µg/ml)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>anticonvulsant, antidysrhythmic</td>
</tr>
<tr>
<td>4</td>
<td>positive inotrope, tinnitus, lightheadedness</td>
</tr>
<tr>
<td>6</td>
<td>vision disturbance</td>
</tr>
<tr>
<td>8</td>
<td>twitching</td>
</tr>
<tr>
<td>10</td>
<td>convulsions</td>
</tr>
<tr>
<td>15</td>
<td>coma</td>
</tr>
<tr>
<td>20</td>
<td>respiratory arrest</td>
</tr>
<tr>
<td>26</td>
<td>cardiac arrest</td>
</tr>
</tbody>
</table>

cardiac
reentrant arrhythmias $\rightarrow$ VF
refractory to DCR

brain
tinnitus, drowsiness, convulsions, coma
worsened by acidosis and hypercarbia due to ion trapping

local neurotoxicity
may be due to preservatives (sodium bisulfite causes permanent damage)

management
correction of acute disturbances
ventilation, oxygen
cardiac massage, DCR, bretylium/lignocaine/lonidine/amiodarone, bypass
correction of acidosis (allows diffusion away from site of action)
control of seizures with benzodiazepine or barbiturate