**Pharm-12B08** Classify the toxic effects of local anaesthetic drugs. Detail the potential for, and mechanisms of, toxicity of prilocaine.

1. **Toxicity** = Unwanted, harmful side effects of a drug
2. Local anaesthetics (LAs) have toxicity that can be classified as:
   a. Local (excessive blockade)
   b. Systemic (blockade of non-target sites) that depends on intrinsic potency & plasma concentration

### 1. Local Toxicity

- **a. Sympathetic chain blockade:** Epidural/spinal blockade inhibits sympathetic preganglionic fibres (type B) → Varying degrees of autonomic dysfunction depending on level of spinal cord:
  - i. High Thoracic → Uncompensated ↓ MAP, CV collapse
  - ii. Low Thoracic → ↓ MAP < ↑ HR with baroreceptor reflex
- **b. Neurotoxicity:** Lignocaine most risk – Neurotoxic concentration that causes irreversible conduction block
  - i. Radicular neuronitis → ↑ Risk with lignocaine (neuronitis <24hrs post spinal that progresses to cauda equina syndrome)
  - ii. Cauda equina syndrome → Inappropriate blockade of lumbosacral plexus → Bilateral leg paraesthesia, weakness, bladder/bowel dysfunction
  - iii. Anterior spinal artery syndrome → Thrombosis/spasm of anterior spinal artery

### 2. Systemic Toxicity

- Follows a usual progression of symptoms/signs & is related to plasma concentration:

<table>
<thead>
<tr>
<th>Lignocaine (µg/mL)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>Analgesia</td>
</tr>
<tr>
<td>5-10</td>
<td>Lightheadedness, numbness of tongue, tinnitus, muscular twitching</td>
</tr>
<tr>
<td>10-15</td>
<td>Seizures, unconsciousness</td>
</tr>
<tr>
<td>15-25</td>
<td>Coma, respiratory arrest</td>
</tr>
<tr>
<td>&gt;25</td>
<td>Cardiovascular depression</td>
</tr>
</tbody>
</table>

- **CNS** – Biphasic response:
  a. Initial excitatory phenomena due to inhibition of inhibitory pathways
  b. Followed by later CNS depression due to inhibition of all pathways
- **CVS** – Bupivacaine > Ropivacaine > Lignocaine
  i. Depressed myocardial conductivity → ↑ PR, QRS, refractory period
  ii. ↓ SVR & myocardial contractility
  iii. Persistent binding to myocardial Na⁺ channels → VT/VF
- **Allergy**
  i. Ester → More likely due to production of para-aminobenzoic acid (PABA)
  ii. Amides → Rare, may occur with preservative (methylparaben)

### 3. Specific Toxicity

- **a. Cocaine** – Ester LA, medium acting, derived from plant
  i. ↓ Reuptake NA+, DA, SHT → CNS excitation → seizures, euphoria, delirium
  ii. Sympathetic stimulation → CVS excitation → ↑ HR, BP, MAP
  iii. Potent vasoconstrictor → CVS coronary artery spasm → AMI, myocardial ischaemia/necrosis
- **b. Prilocaine** – Amide LA, short acting
  i. Methaemoglobinemia: Metabolised in liver to o-toluidine → Oxidises Fe²⁺ of Hb to Fe³⁺ → MetHb → Unable to bind or transport O₂
  ii. Hypoxia & central cyanosis refractory to oxygen therapy

### 4. Factors Affecting Toxicity

- Systemic toxicity directly related to plasma concentration of drug → Influenced by pharmacodynamic, pharmacokinetic & patient factors:
  - **Administration factors:**
    1. Dose/concentration: Toxicity related to peak & rate of rise of plasma concentration → ↑ Dose → ↑ Concentration → ↑ Toxicity
    2. Site of administration: ↑ Vasularity → ↑ Systemic absorption (intrapleural > intercostal > caudal > brachial plexus > femoral/sciatic > S/C > topical)
  - **Additives:**
     - Adrenaline – Local vasoconstriction → ↓ Local blood flow → ↓ Systemic uptake → ↓ Toxicity
     - Other LAs → CNS/CVS toxic effects are additive
  - **Drug factors:**
    1. Lipid solubility: Determines potency which affects the threshold plasma concentrations at which toxicity occurs
      - ↑ Lipid solubility → ↑ LA movement into tissues

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxic Plasma Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>3</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>4</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>5</td>
</tr>
</tbody>
</table>

- **2. Duration of binding:** longer Na⁺ channel binding → longer duration of action → greater toxicity potential
- **3. Vasoactivity:** Low doses cause vasodilation → ↑ Blood flow → ↑ Systemic absorption → ↑ Toxicity (prilocaine > lignocaine > bupivacaine > ropivacaine > cocaine)
- **4. Isomerism:** R-enantiomer generally more toxic than S-enantiomer (e.g. levobupivacaine vs bupivacaine)
- **5. CVS:CNS ratio:** ratio of concentration to cause arrhythmia to concentration to cause seizure. Higher the CVS:CNS ratio, earlier CNS warning re: toxicity → safer e.g. CVS:CNS ratio for lignocaine = 7, ropivacaine = 3, bupivacaine = 2
- **6. Metabolism/clearance:** ↑ Clearance → ↓ Plasma concentration → ↓ Toxicity:
- Esters: Metabolised by plasma esterases in peripheral tissues → Fast metabolism → ↓ Toxicity (except cocaine which is hepatically metabolised → ↑ Toxicity)
- Amides: Metabolised by hepatic amidases → Longer half life → ↑ Risk plasma accumulation

<table>
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<tr>
<th>Drug</th>
<th>Clearance (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>0.47</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.44</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Patient factors:

1. Acidosis: Acidic environments → ↑ Ionised fraction → Ion trapping within axoplasm → ↑ Toxicity to organs where trapped (e.g. fetal acidosis → fetal LA toxicity)
2. Pregnancy: Progesterone competes with LA for binding of α₁-acid glycoprotein → ↑ Free drug → ↑ Toxicity
3. Disease states: Cardiac/hepatic/renal dysfunction → ↓ Metabolism/elimination → ↑ Duration ± accumulation of active metabolites → ↑ Toxicity
4. Obesity: Fat acts as reservoir for lipid soluble drugs → ↓ Systemic toxicity
5. Electrolytes: ↑ K⁺, ↓ Ca²⁺ → Hyper-excitable membrane → ↑ Toxicity