

Q22 Describe the factors that increase the risk of systemic toxicity of the amide local anaesthetics (Sept 2012)

Local anaesthetics – agents used to inhibit transmission of painful afferent signals to the cortex.

Signs of toxicity may be seen at plasma lignocaine concentrations of 2mcg/ml (tinnitus, circumoral numbness), progressing to convulsions at 10mcg/ml, respiratory arrest at 20mcg/ml and CVS collapse at 26mcg/ml. The degree of toxicity is related to the absolute blood level, the rate of change of the blood level, and pre existing CVS/CNS disease.

Factors increasing the risk of systemic toxicity:

1. DRUG FACTORS

- CNS:CVS ratio → dose ratio of CNS symptom onset (reversible) to CVS symptom onset (life threatening, refractory) is a measure of safety. Lignocaine 7, ropivacaine 4, bupivacaine 3
- Isomerism → pure enantiomers have a better safety profile than racemic mixtures (bupivacaine S-enantiomer fewer side effects than racemic bupivacaine)
- Lipophilicity → more lipid soluble drugs will be absorbed faster
- pKa → the LA's are weak bases with relatively high pKa's; the lower the pKa the more unionized (thus increasing the amount available for systemic absorption). Lignocaine pKa 7.9 (25% unionized at pH 7.4), bupivacaine pKa 8.4, 11% unionized at 7.4
- Intrinsic vasoactive properties → in general cause vasodilatation at low doses (thus increasing the risk of systemic toxicity) and vasoconstriction at high doses
- Co administration with vasoconstrictor → reduces diffusion away from the target site thus reducing systemic toxicity
- Protein binding → more protein binding in tissues reduces systemic absorption; once in the plasma, highly protein bound drugs have a smaller free fraction available to cause effects; once in the CNS/CVS, high protein binding prolongs toxicity
- Dose → The greater the dose, the higher the risk of toxicity
- Concentration → higher conc maintains the conc gradient between tissue and plasma, increasing systemic absorption
- Relative potency → relative toxicity approximates the relative potency of the agent used
- Mechanism → all act via binding to and inactivating sodium channels, however bupivacaine is ten times slower at dissociating from the channel than lignocaine is

2. PATIENT FACTORS

- Cardiac output / regional blood flow → determines the movement of drug away from the injection site to the systemic circulation
- Hepatic function – the amides are metabolized by the liver, hence liver dysfunction will prolong the half life and potentiate toxicity. Liver dysfunction may also reduce plasma proteins hence increased free fraction of drug
- Renal dysfunction → reduced clearance of drugs with active metabolites (eg ropivacaine)
- Acidaemia → lower pH increases the ionization of LA's and traps them within the cell → increases toxicity if in CNS/CVS
- PaCO₂ → inversely related to the convulsive threshold (b/c increasing PaCO₂ increases cerebral blood flow and delivery of agent to brain)

3. SITE OF INJECTION

- Absorption of LA's into the systemic circulation varies depending on the site of injection → (intercostal>epidural>brachial plexus>subcutaneous infiltration)
- Inadvertent IV injection will increase toxicity

4. OTHER

- Drug interactions → inhibition of CYP450 system (eg various antibiotics, amiodarone), competition for protein binding