Episode 19 - Local Anaesthetics Pharmacology

Basic structure

Aromatic group (lipophilic)
Intermediate chain (ester or amide bond)
Tertiary amine group (hydrophilic)

Ester and amide local anaesthetics

The type of intermediate chain (ester or amide bond) affects metabolism, duration of action and likelihood of allergic reactions. Both types contain a C=O bond. The names of the amide local anaesthetics contain two letter "i"s.

Ester ($COOCH_2$)	Amide ($NHCOCH_2$)
Procaine Cocaine Tetracaine (Amethocaine) Proparacaine	Lidocaine (Lignocaine) Bupivacaine Ropivacaine Prilocaine Mepivacaine Articaine Dibucaine Etidocaine

Articaine

Commonly used in dentistry. It is unique in that it has a sulphur-containing thiophene ring rather than the usual benzene ring of other local anaesthetics (making it more lipid soluble). It also contains an extra ester group (attached to this ring) which means that it is rapidly metabolised by tissue and plasma esterases.

Metabolism

Ester local anaesthetics	Plasma butyrylcholinesterase (pseudocholinesterase)
Amide local anaesthetics	Liver cytochromes phase I oxidation

Note: Ester local anaesthetics are broken down by plasma cholinesterase to produce paraaminobenzoic acid (PABA) which is highly antigenic and gives rise to allergic reactions.

Enzyme	Drugs
Plasma butyrylcholinesterase (pseudocholinesterase)	Suxamethonium (Succinylcholine) Mivacurium Ester local anaesthetics
Non-specific tissue and plasma esterases	Remifentanil
Cytosolic esterases (in red blood cells)	Esmolol

Properties

- Potency determined by lipid solubility
- Speed of onset determined by pKa
- Duration of action determined by protein binding

Drug	Potency (lipid solubility)	Speed of onset (pKa)	Protein binding	Half-life (elimination)
Procaine	Lowest	8.9	5%	10 min
Cocaine	Moderate	8.6	95%	1 hour
Tetracaine	Highest	8.5	75%	2-3 hours
Lidocaine	Moderate	7.9 (fast)	70% (short)	1.5-2 hours
Bupivacaine	High	8.1	95%	3 hours
Ropivacaine	High	8.1	95%	2 hours
Prilocaine	Moderate	7.9 (fast)	50%	1.5-2 hours

Note: the most relevant comparison is between Lidocaine and Bupivacaine/Ropivacaine.

Speed of onset

Speed of onset is determined by pKa and its relation to the pH of normal body fluids (pH 7.40). All local anaesthetics have a pKa greater than this; they are weak bases and are ionised at physiological pH. Weak bases are ionised when they gain a hydrogen ion, H^+. The more ionised they are the less able to cross cell membranes and the slower their onset of action.

Dosing and frequency

Drug	Maximum Dose	Duration of action	Dosing interval (minimum)
Procaine	-	30-60 minutes	1 hour
Cocaine	3 mg/kg	30-90 minutes	Not repeated.
Tetracaine	-	2-4 hours	4 hours
Lidocaine	3 mg/kg	1-2 hours	3 hours
Bupivacaine	2 mg/kg	4-6 hours	6 hours
Ropivacaine	2 mg/kg	4-6 hours	6 hours
Prilocaine	6 mg/kg	1-2 hours	3 hours

Note: figures in this table have been simplified.