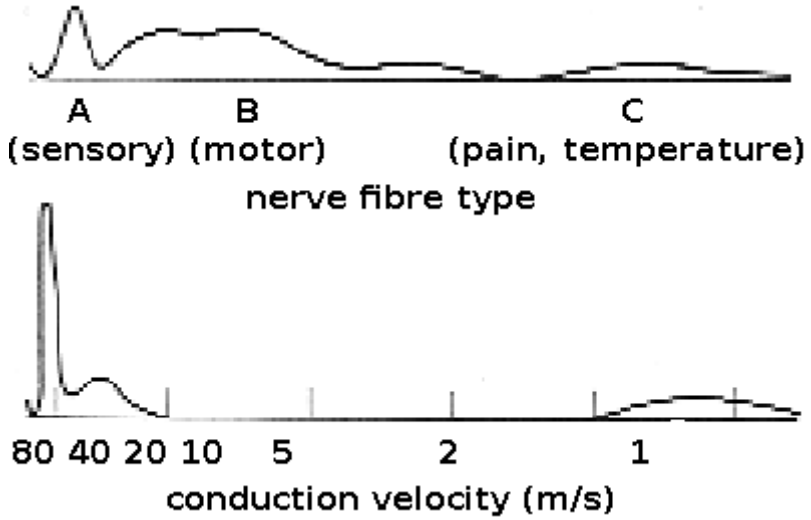
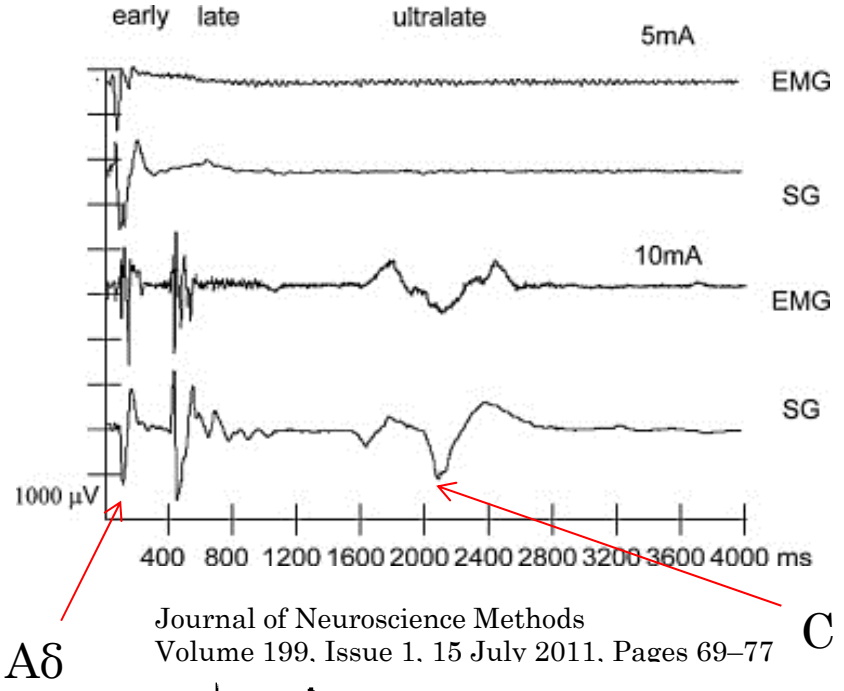
Local anesthetics

Table 3: Types of neurons blocked with local anesthetics

Neuron type	Function	Myelination	Order of Blockade	Signs of Blockade
A alpha	Motor -skeletal muscle	Myelinated	Fifth	Loss of motor function
A beta	Sensory – touch, pressure	Myelinated	Fourth	Loss of sensation to touch and pressure
A gamma	Motor - muscle spindles proprioception	Myelinated	Third	Loss of proprioception
A delta	**Fast pain temperature**	**Myelinated**	**Second**	**Pain relief, loss of temperature sensation**
B	Autonomic, Pre-ganglionic sympathetic	Myelinated	First	Increased skin temperature
C	**Slow pain, autonomic, postganglionic sympathetic, polymodal nociceptors**	**Unmyelinated**	**Second**	**Pain relief, loss of temperature sensation**





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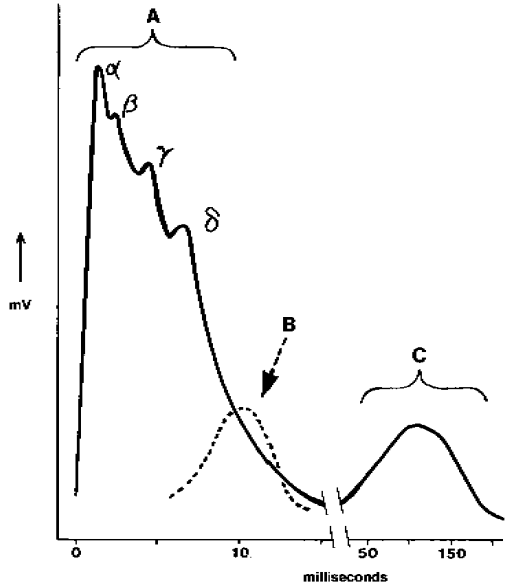
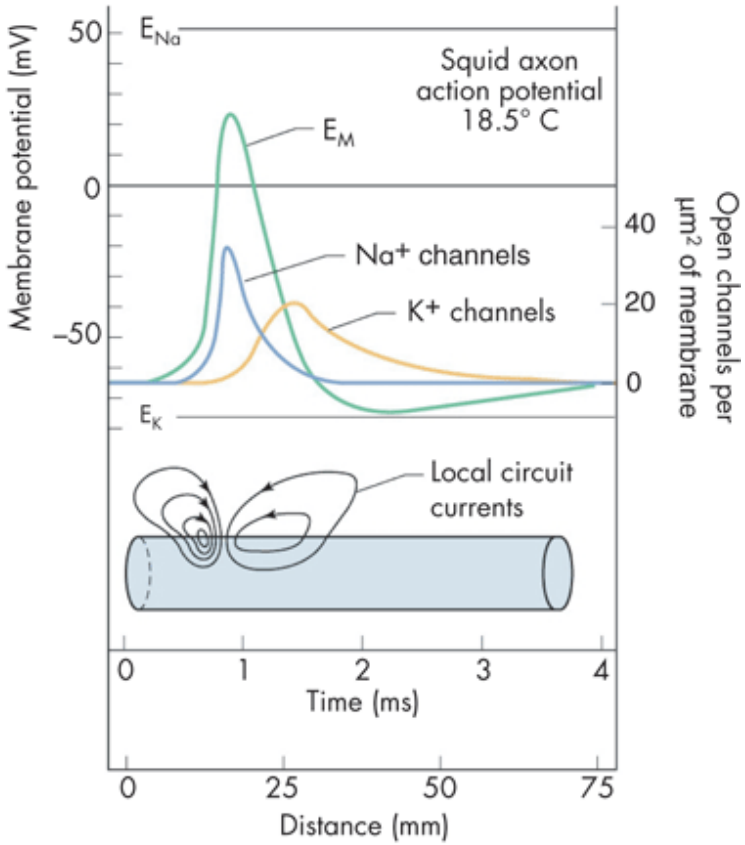


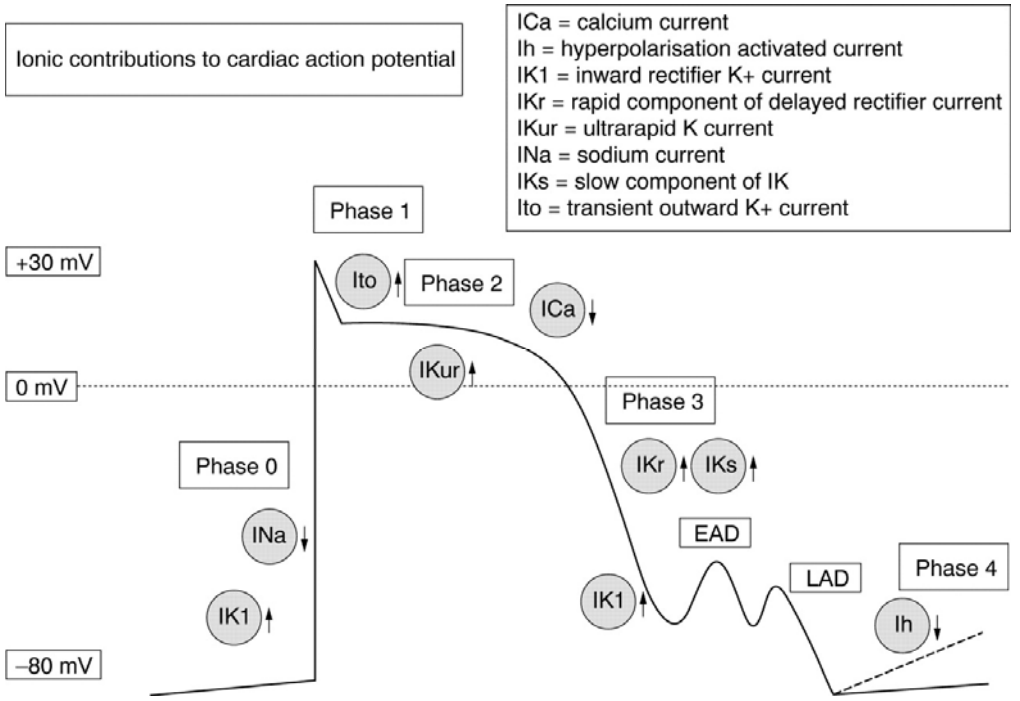
Fig. 6. A compound action potential, as recorded from a nerve in a limb of any mammal. The B wave, due to preganglionic autonomic fibres, would not be recorded from such a nerve.

Ionic currents during action potentials



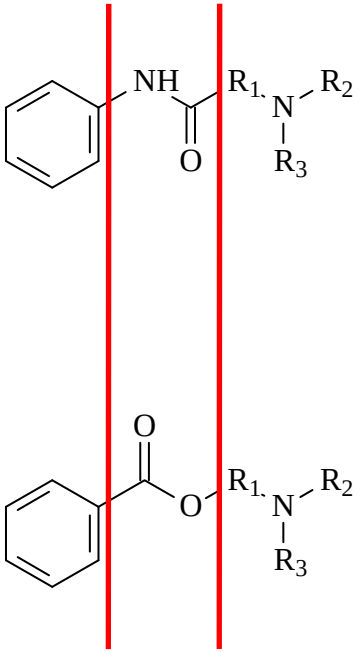
A

B

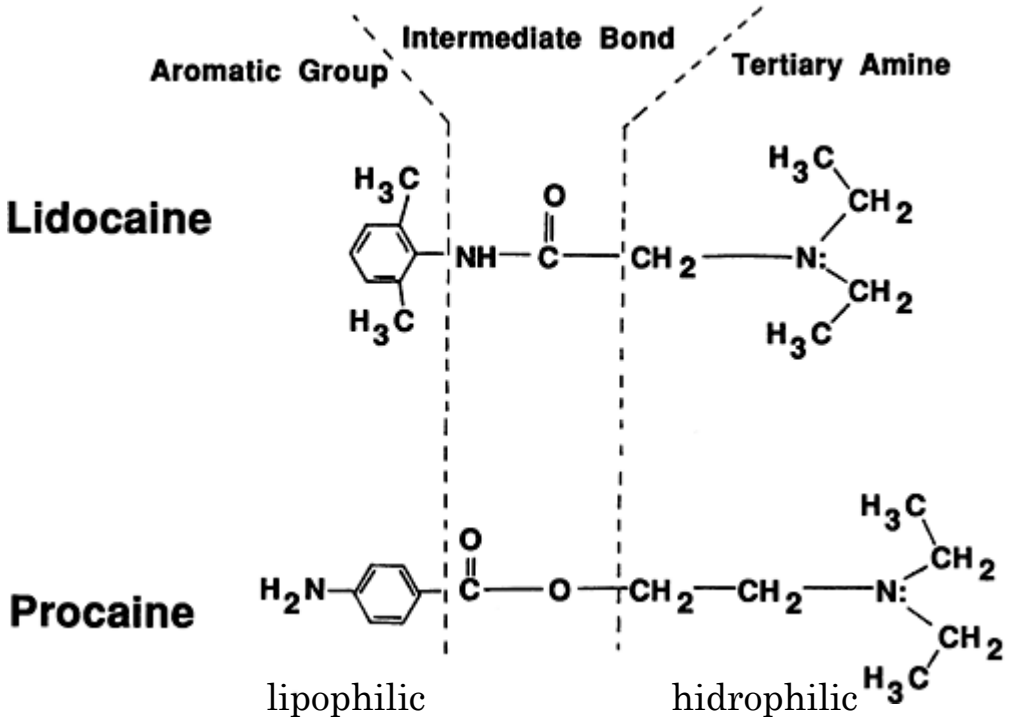


Chemical structure

Aminoamide linkage



Aminoester linkage



Background

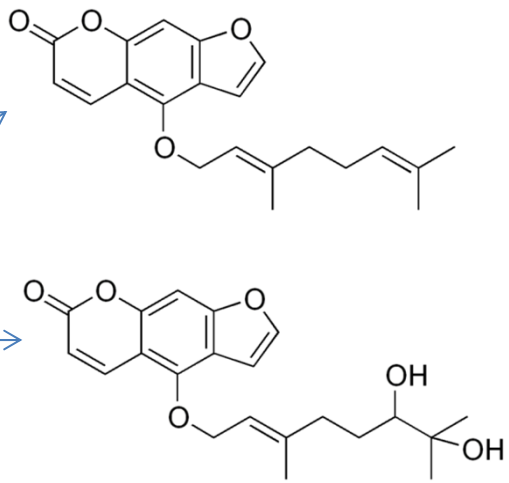
- Erythroxylon coca (1860) → cocain
  - Sigmund Freud, Karl Koller 1884

Ester compounds

- 1905 Einhorn introduces the prototypical ester local anesthetic procaine.
- Metabolization: pseudocholinesterase in plasma
- Metabolite: para-aminobenzoic acid (PABA) → allergene
- Short acting
- Weak bases

Amide derivatives

- Lofgren 1943 → lidocain
- Metabolization: P-4503A4
  - Small intestine (inhibitor: grapefruit juice (furanocoumarins (bergamottin, dihydroxybergamottin)))
  - Liver (inhibitors: itrakonazole, ketokonazole, erythromycin, clarithromycin, cyclosporin, indinavir, ritonavir, diltiazem, mibefradil, nefazodone)
- Long acting
- Weak bases



Rate of metabolism: prilocaine> lidocaine> mepivacaine> ropivacaine> bupivacaine.

Differences in nomenclature

- Amides will contain an “i” in the generic name prior to “-caine”. (i.e. lidocaine, mepivacaine, prilocaine, bupivacaine, ropivacaine, and levo-bupivacaine).
- Ester’s do not contain an “i” in the generic name prior to “-caine”. (i.e. procaine, chloroprocaine, cocaine, benzocaine, and tetracaine).

Factors that affect potency of local anesthetics

- Hydrophobicity (lipid solubility)
- Hydrogen ion balance
- Vasoconstrictor/vasodilator properties (affects the rate of vascular uptake)
- Fiber size, type, and myelination
- Frequency of nerve stimulation
- pH (acidic environment will antagonize the block)
- Electrolyte concentrations (hypokalemia and hypercalcemia antagonizes blockade).

Lipophilic-Hydrophobic Balance- Potency and Lipid Solubility/Duration of Action

Local Anesthetic	Potency and Lipid Solubility/Duration of Action
AMIDES	
Bupivacaine and levo-Bupivacaine	4/4
Etidocaine	4/4
Lidocaine	2/2
Mepivacaine	2/2
Prilocaine	2/2
Ropivacaine	4/4
ESTERS	
Chloroprocaine	1/1
Cocaine	2/2
Procaine	1/1
Tetracaine	4/3

1= least; 4= greatest

Ionized vs Non-ionized forms

- Non-ionized: penetrates the cell membranes
- Ionized: blocks the Na^+ channel

pKa of Local Anesthetics

Local Anesthetic	pKa
AMIDES	
Bupivacaine and levo-Bupivacaine	8.1
Etidocaine	7.7
Lidocaine	7.8
Mepivacaine	7.6
Prilocaine	7.8
Ropivacaine	8.1
ESTERS	
Chloroprocaine	9.0
Cocaine	8.7
Procaine	8.9
Tetracaine	8.2

- Local anesthetics are prepared in a water soluble HCL salt with a pH of 6-7.
- If epinephrine is added, in a commercial preparation, the pH is kept between 4-5 to keep epinephrine stable. This creates less free base (non-ionized) and slows the onset of action.

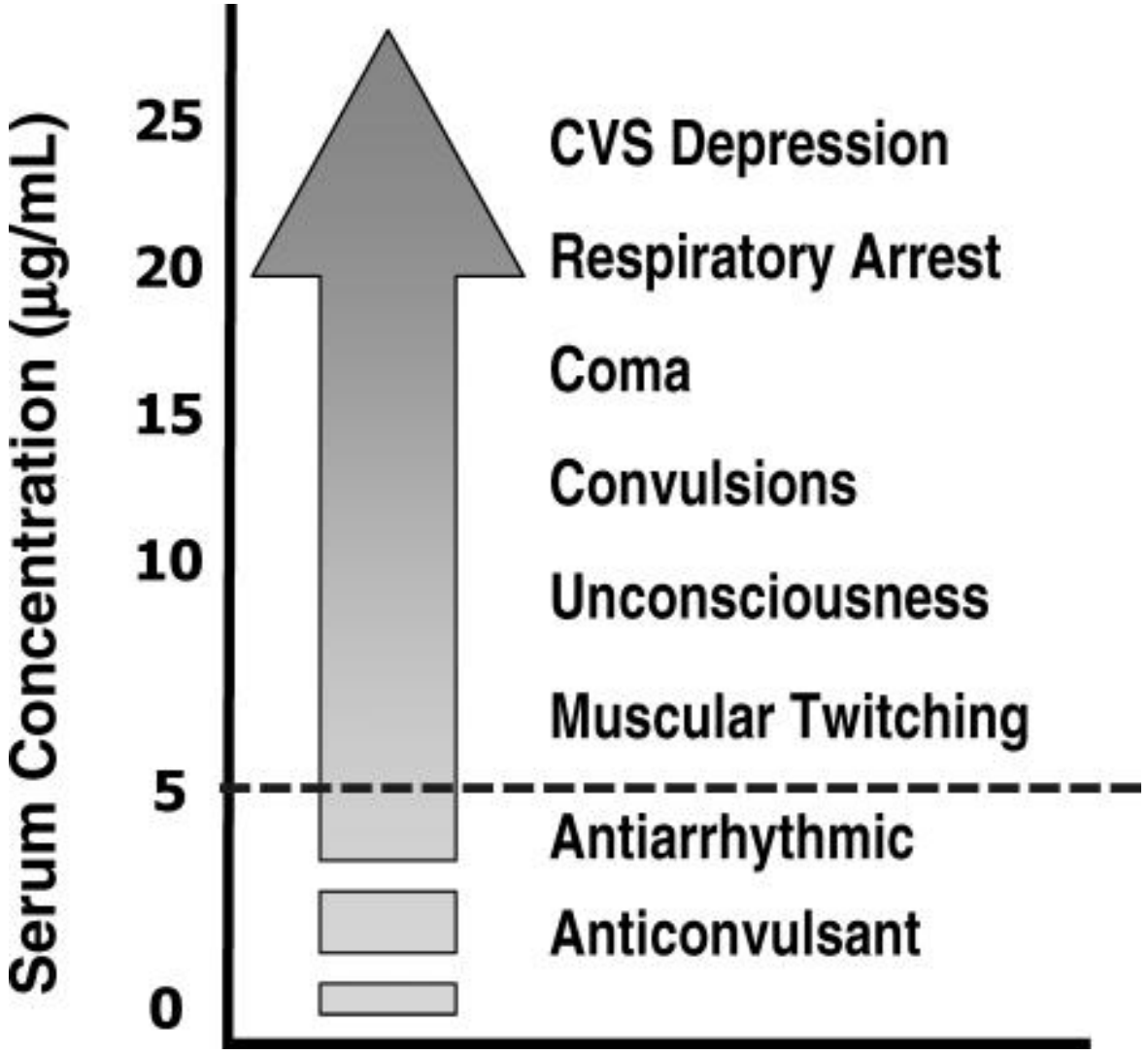
Clinical Implications of Ionized and Non-ionized Forms of Local Anesthetic

- Local anesthetics are prepared in a water soluble HCL salt with a pH of 6-7.
- If epinephrine is added, in a commercial preparation, the pH is kept between 4-5 to keep epinephrine stable. This creates less free base (non-ionized) and slows the onset of action.
- Some clinicians will add NaBicarb to commercially prepared solutions that contain epinephrine to increase the amount of free base (non-ionized form).
- 1 ml of 8.4% NaBicarb to each 10 ml of lidocaine or mepivacaine or 0.1 ml of 8.4% NaBicarb to each 10 ml of bupivacaine.
- If you add more NaBicarb than suggested the solution will precipitate.

Reported Benefits of adding Sodium Bicarbonate

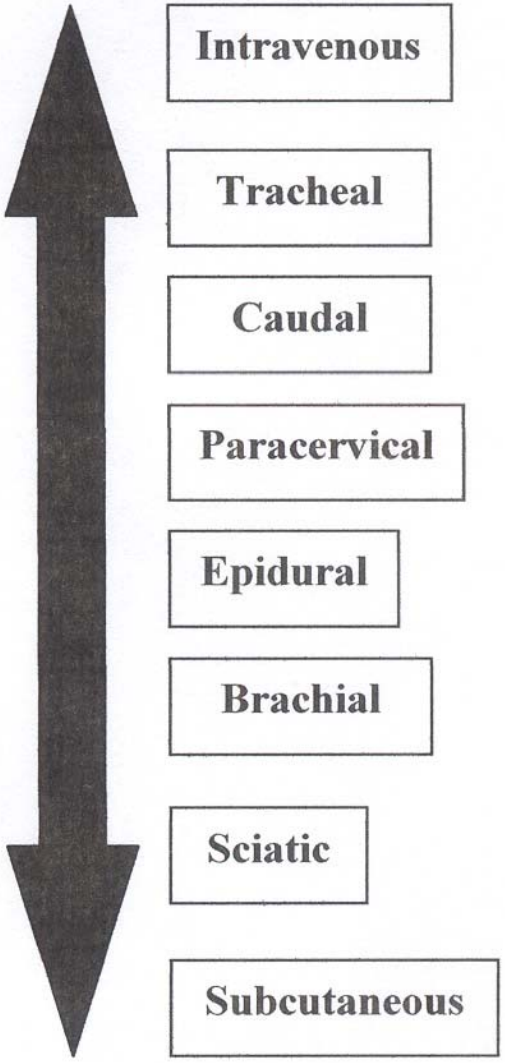
- Increases the amount of free base (non-ionized form of local anesthetic)
- Speed onset
- Improve quality of the block
- Prolongs the duration of blockade
- Decreased pain associated with subcutaneous infiltration

Systemic influences of lidocaine

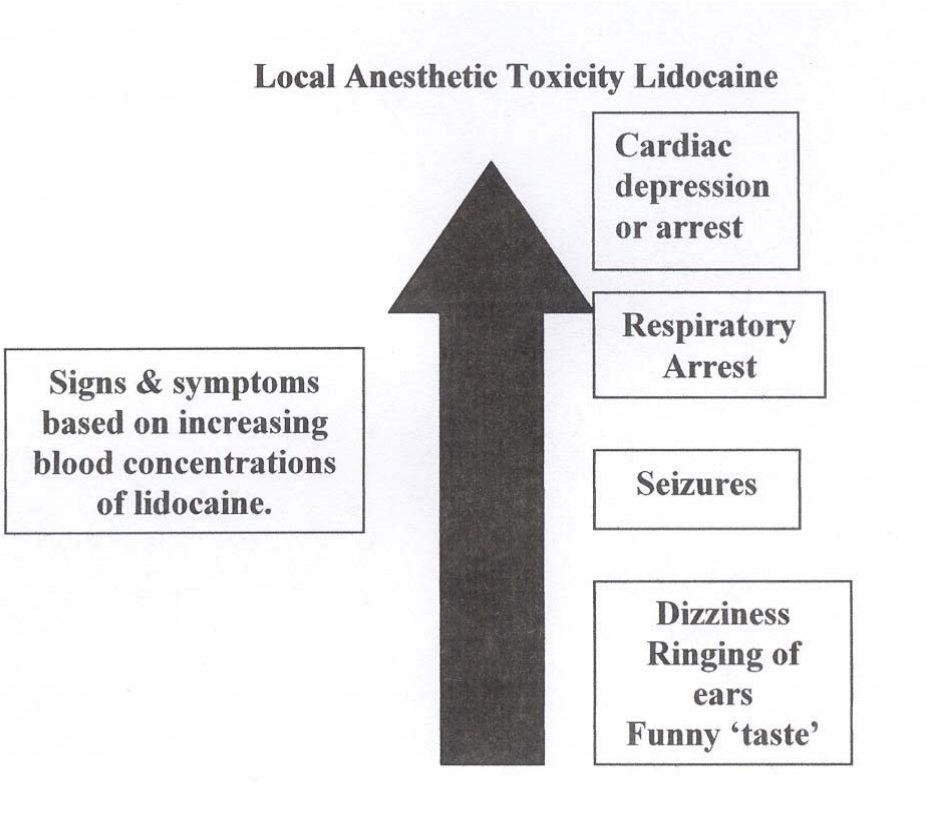


Uptake of Local Anesthetics Based on Regional Anesthesia Technique

Result in Highest Blood Concentrations



Lower Blood Concentrations



- More later but signs and symptoms vary among local anesthetics…
- With lidocaine there is a large disparity in blood concentrations between CNS signs and symptoms (which occur at lower blood concentrations and cardiovascular collapse)
- Benzocaine can cause methemoglobinemia.
- Ester local anesthetics placed in the CSF are not metabolized until absorbed by the vascular system. No esterase enzymes in the CSF.

Duration of Action: Classification of Local Anesthetics

- Short acting: procaine, chloroprocaine
- Moderate acting: lidocaine, mepivacaine, prilocaine.
- Long acting: tetracaine, bupivacaine, etidocaine

SOURCE OF DIFFERENCES
Local anesthetics exhibit a biphasic effect on vascular smooth muscle.
Low sub-clinical doses vasoconstriction occurs.
Clinically relevant doses generally cause vasodilatation.

Medication Interactions with Local Anesthetics

Ester Local Anesthetics	Succinylcholine- may potentiate the effects since both are dependant on pseudocholinesterase for metabolism.
Ester Local Anesthetics	Cholinesterase inhibitors such as neostigmine and pyridostigmine can lead to a decrease in the metabolism of ester local anesthetics.
Local Anesthetics in General	Opioids and alpha adrenergic agonists potentiate the analgesic effects of local anesthetics.
Local Anesthetics in General	Potentiate the effects of non-depolarizing muscle relaxant blockade.
Chloroprocaine (epidural)	May interfere with the analgesic effects of subarachnoid opioids.
Lidocaine	Cimetidine and propranolol decrease hepatic blood flow and lidocaine clearance. This acts to increase the risk of systemic toxicity.

Further reading: Daniel E Becker, DDS and Kenneth L Reed, DMD: Essentials of Local Anesthetic Pharmacology. Anesth Prog. 2006 Fall; 53(3): 98–109.