Local anaesthetics

Dr JM Dippenaar

Chemical structure

Lipophilic phenol ring

+

Amide/Ester bridge

+

Hydrophilic chain

Local anesthetic drugs

Amides

Lignocaine

Bupivacaine

Ropivacaine

Levobupivacaine

mepivacaine

Esters

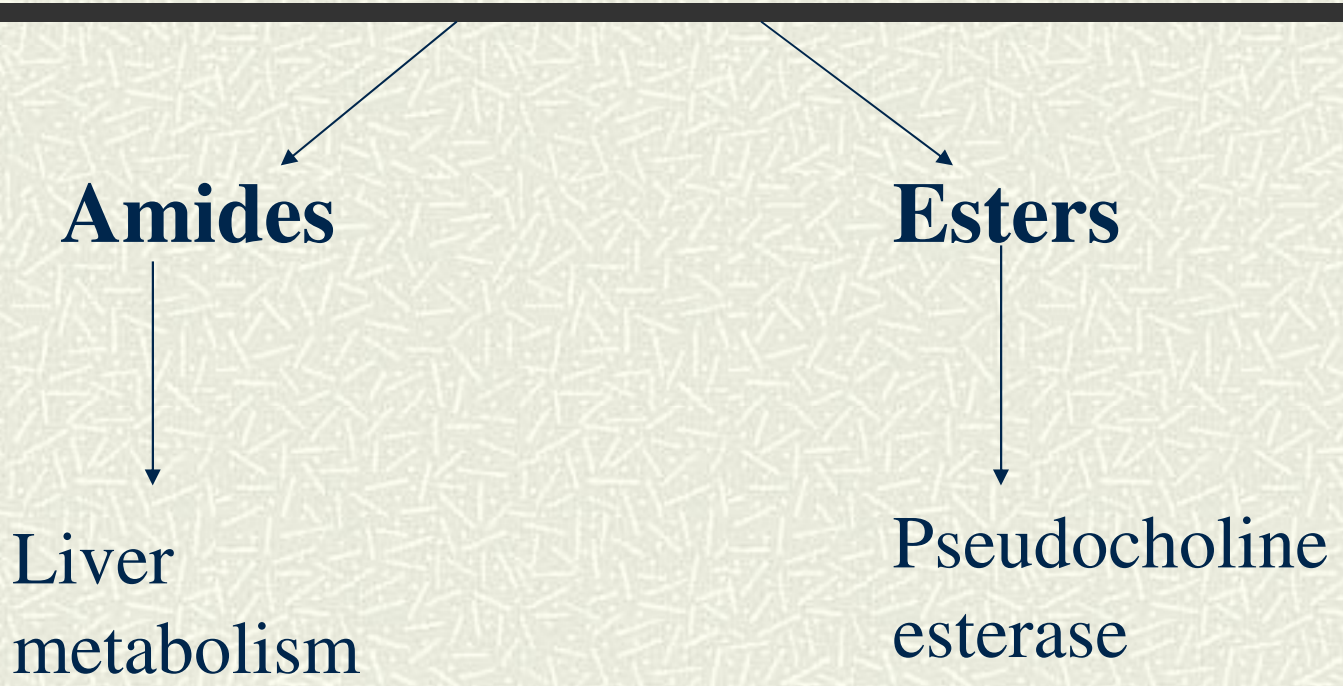
Cocaine

PABA esters

Procaine

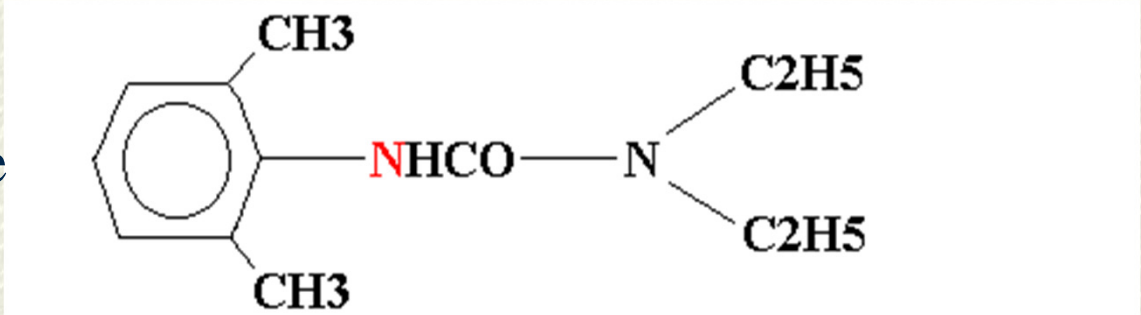
Chloroprocaine

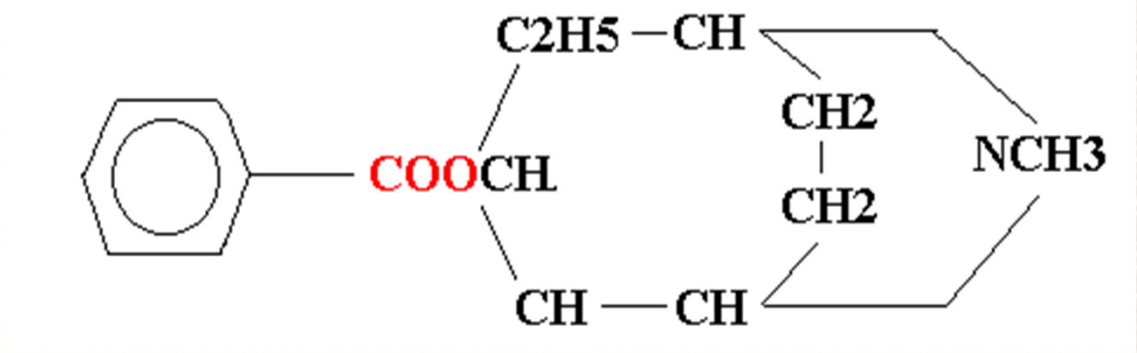
Local anesthetic drugs



Local anesthetic drugs

Lignocaine

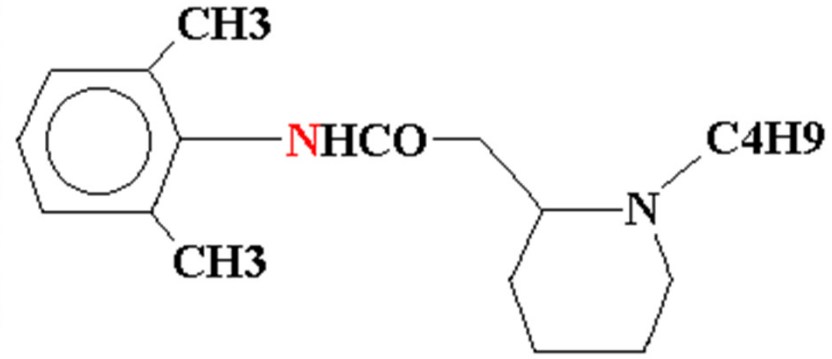


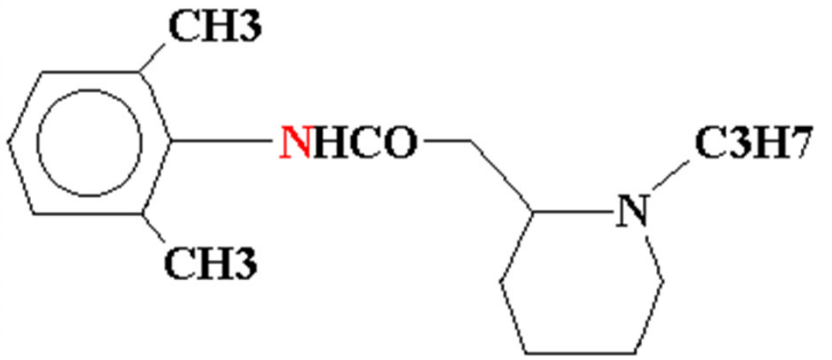


Cocaine

Local anesthetic drugs

Bupivacaine



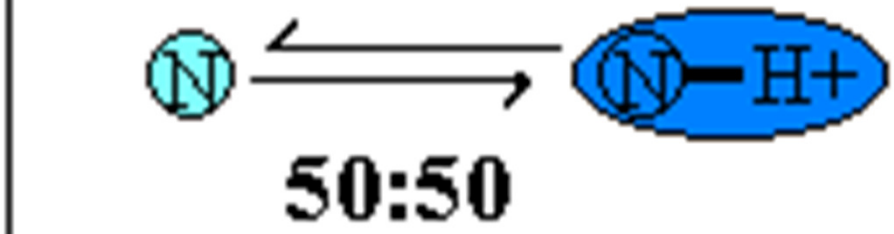


Ropivacaine

Chemical & physical characteristics

- Lipid solubility = potency
- $\propto$ onset of action
- pKa $\propto$ onset of action

pKa



pH = 8.1

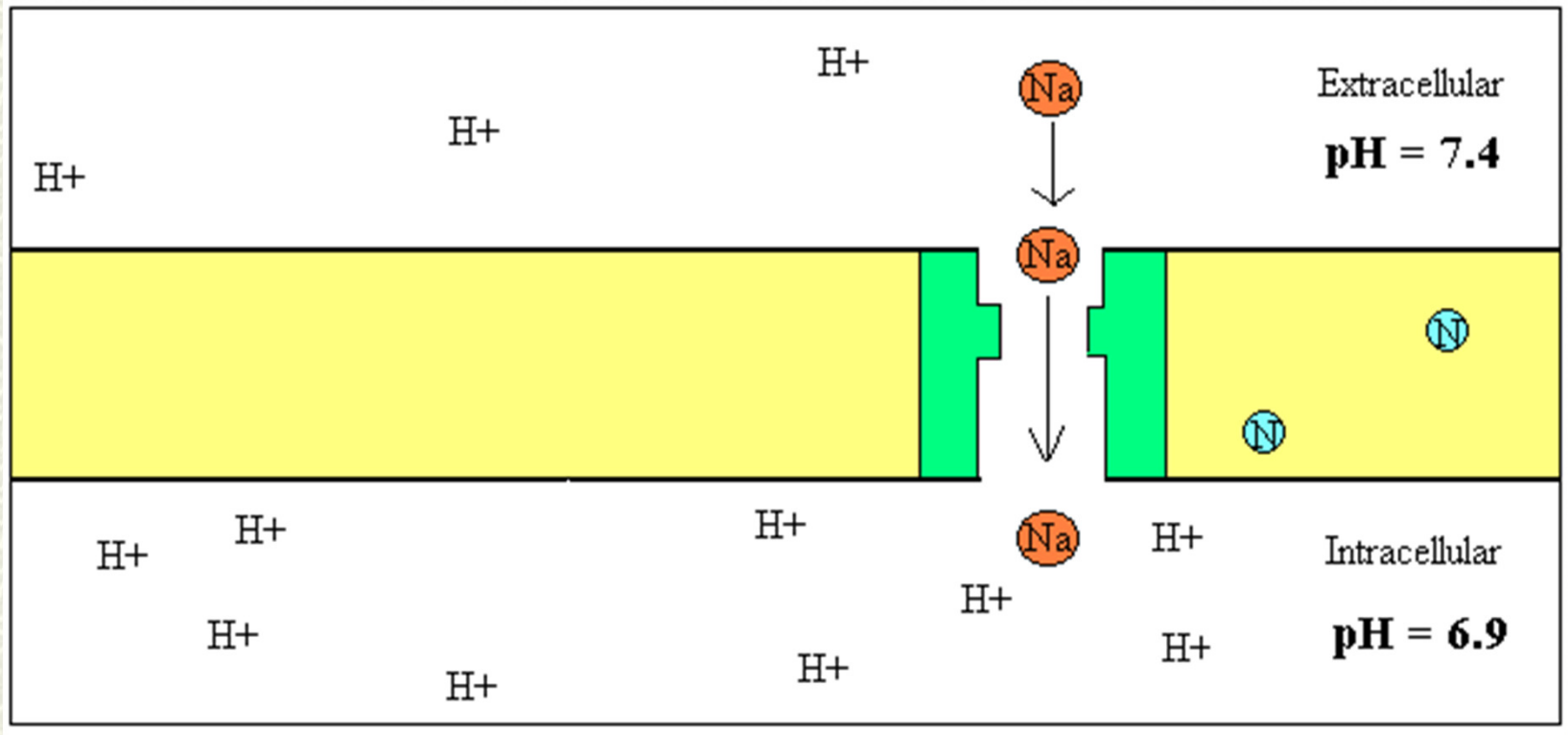
Chemical & physical characteristics

- Lipid solubility = potency, ∝ onset of action
- pKa ∝ onset of action
- Protein binding = duration of action
- Isomerism – L=↑ duration, potency,↓ toxicity
- Local factors – spinal vs. peripheral
- Nerve anatomy
  - Diameter, myelinated or not, activity

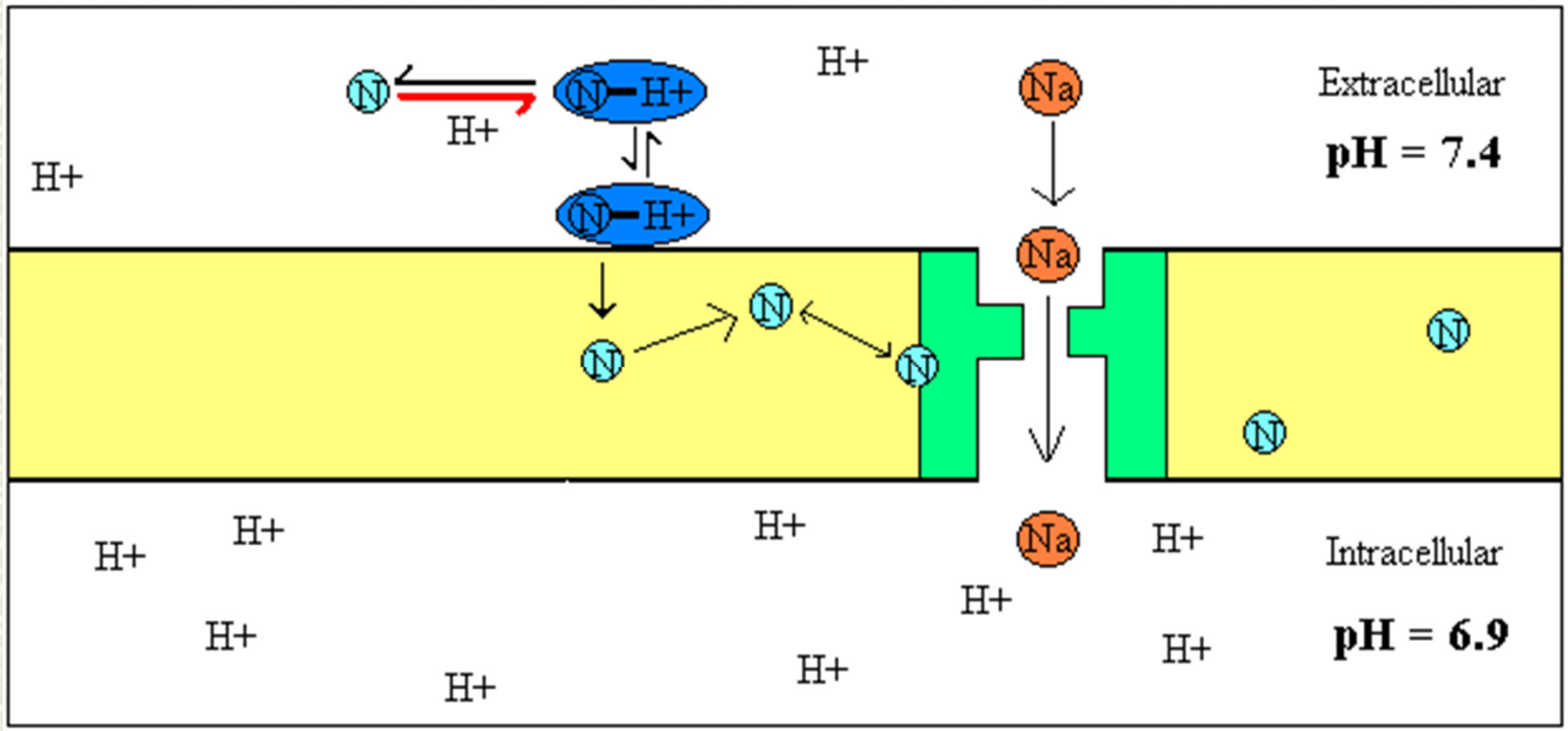
Physico-chemical properties

Drug	Lipid solubility	pKa	Protein binding	Potency
Lignocaine	2.9	7.7	64	4
Bupivacaine Levo-bupiva	27	8.1 8.1	95.5 94.3	16
Ropivacaine	25	8.1	94.	16

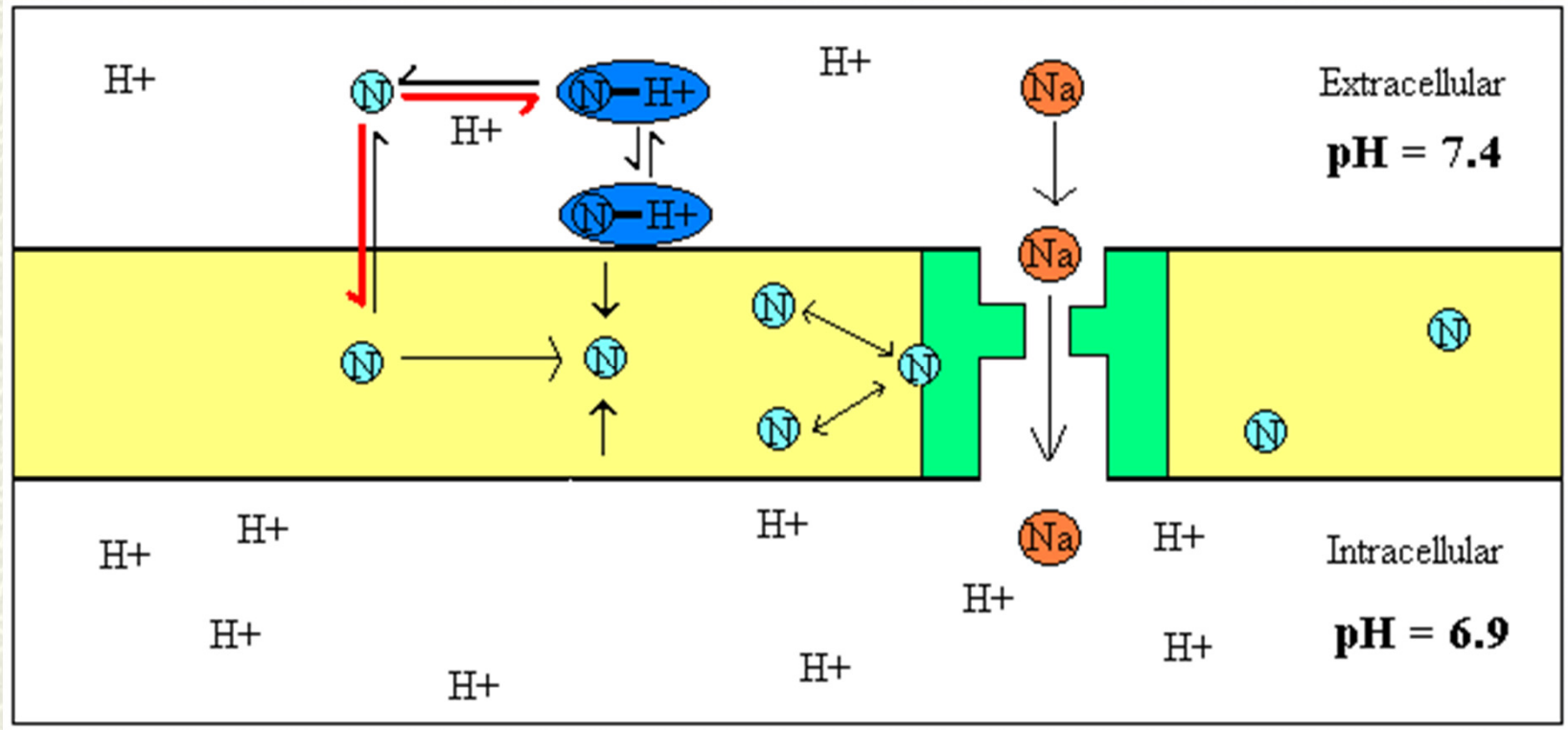
Mechanism of action



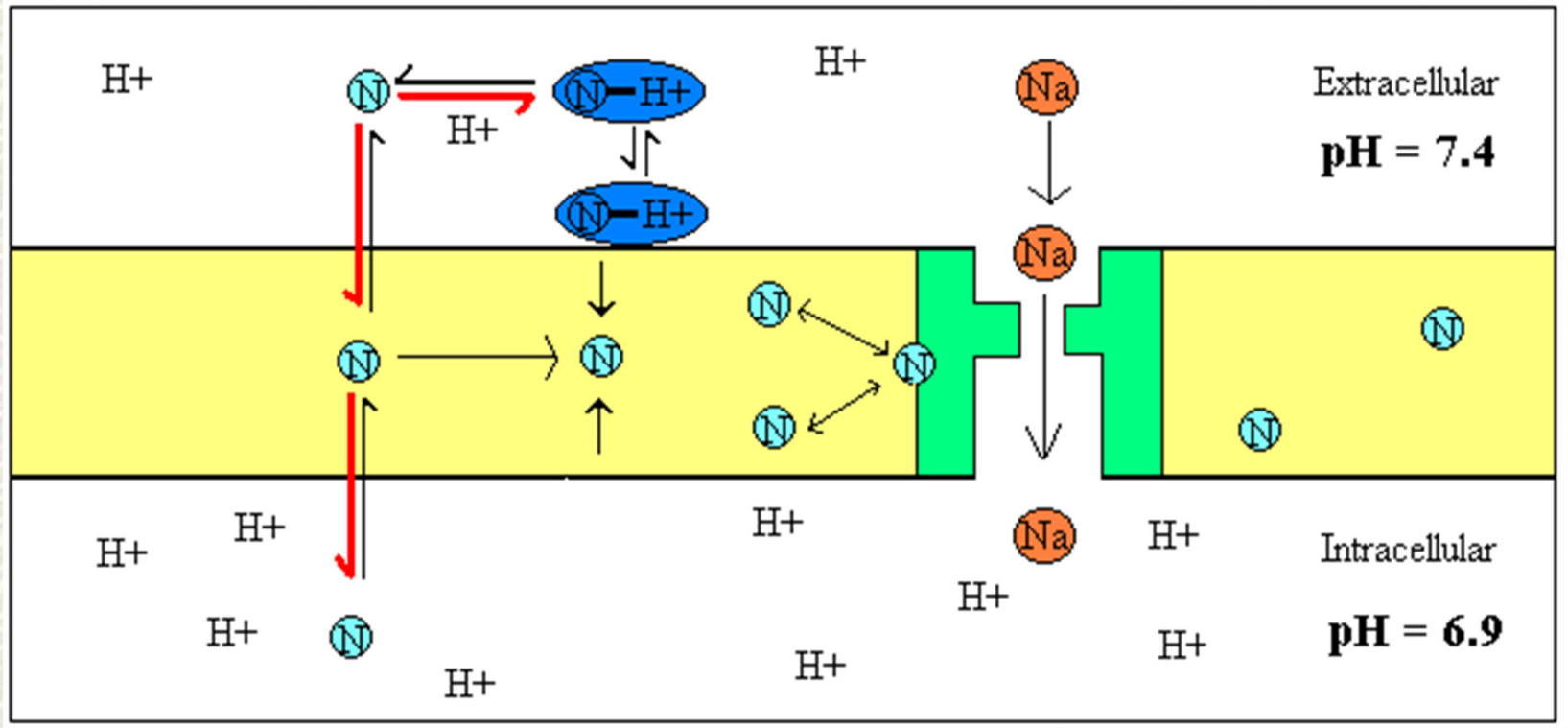
Mechanism of action



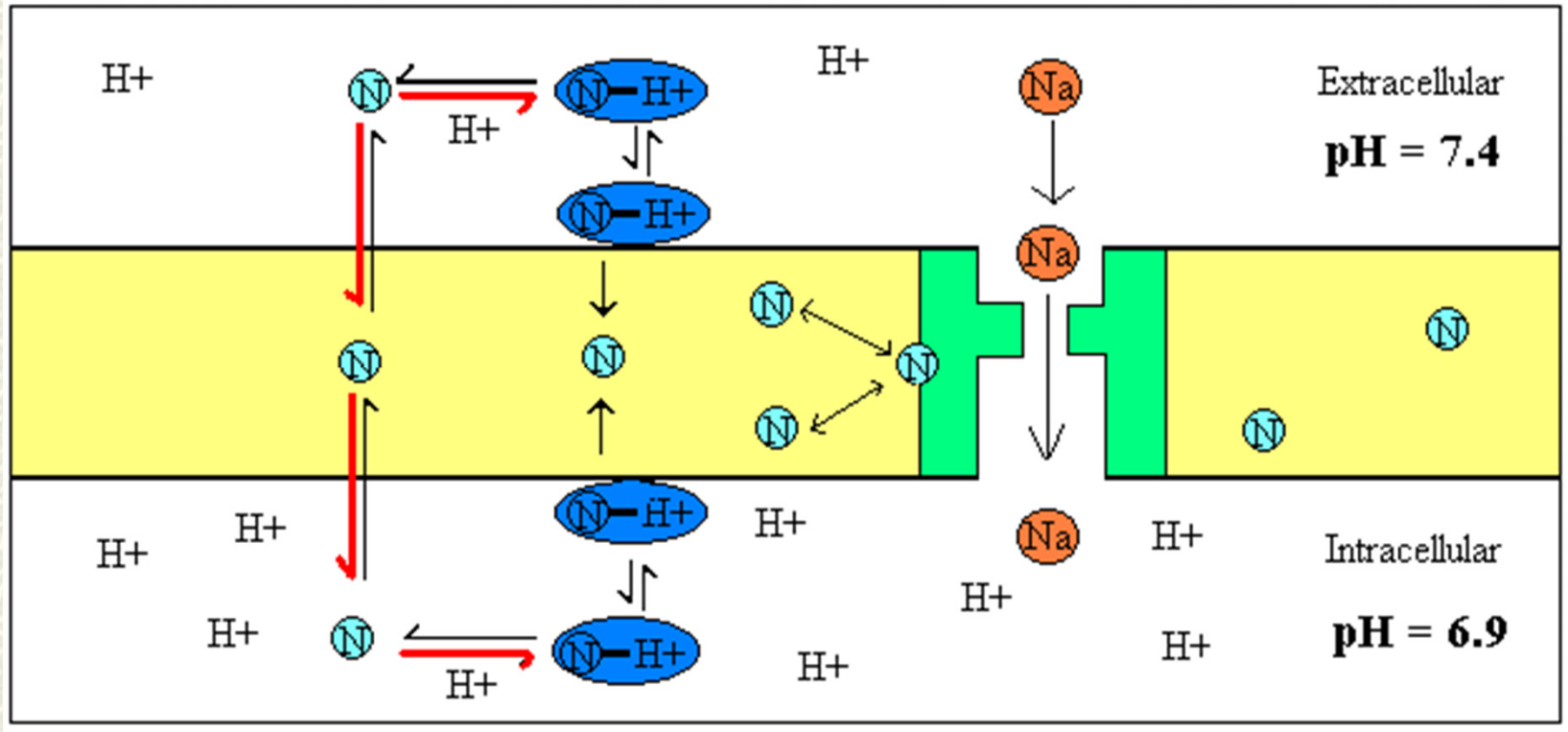
Mechanism of action



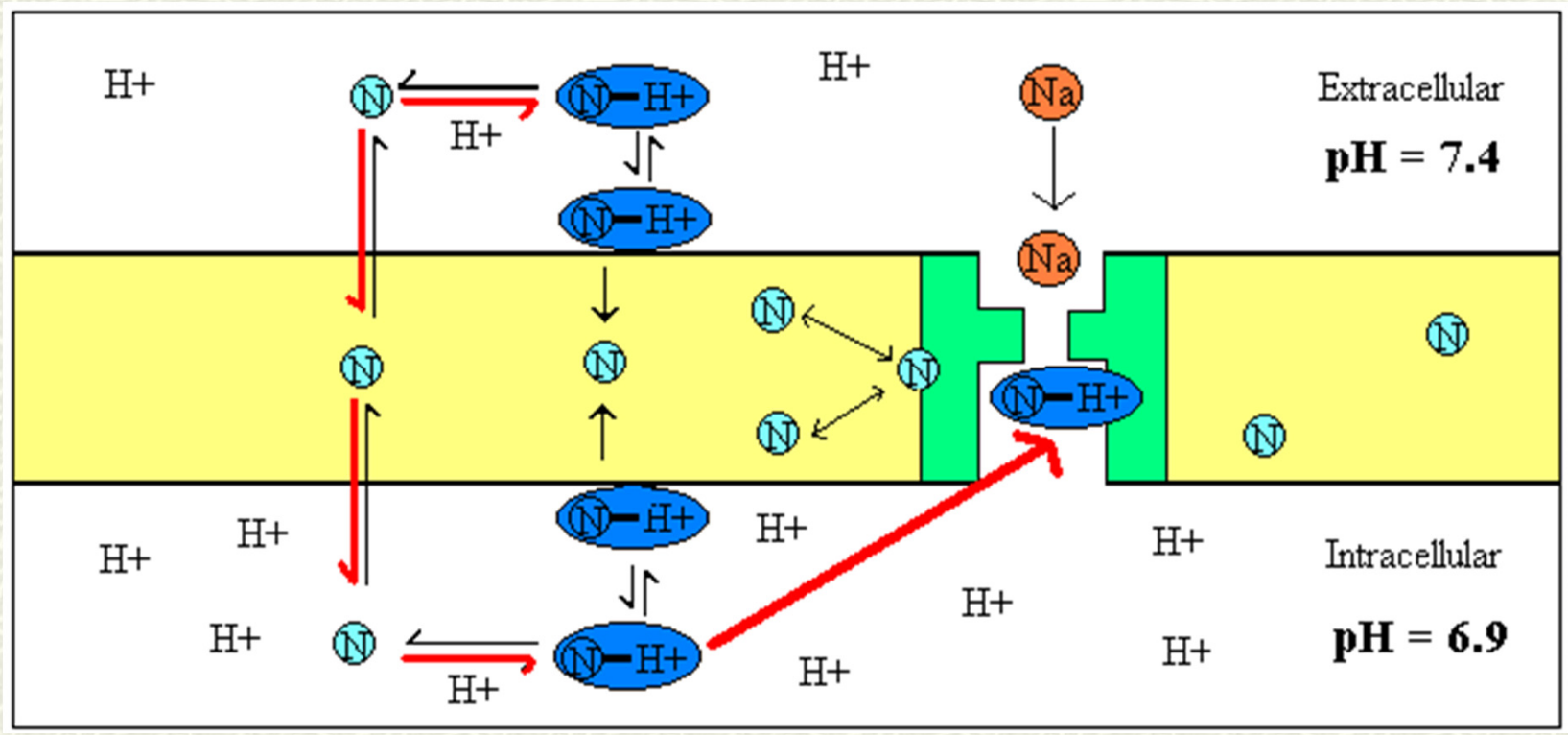
Mechanism of action



Mechanism of action



Mechanism of action



Cocaine

- Ester derivative
- Intense vasoconstriction
- Indirect sympathomimetic
  - release NA
  - Block reuptake of NA and dopamine
- S/E
  - Euphoria, paranoia, seizures,
  - Hypertension, tachcardia

Prilocaine

- **Emla** cream
  - **E**utetic **M**ixture of **L**ocal **A**naesthetic
  - Added to lignocaine in equal quantities
  - Changes the melting point of the drugs
  - Skin analgesia within 60 min
- **Methaemoglobinaemia**

Lignocaine

- Amide , pKa = 7.7
- Low lipid solubility
- Metabolism
  - Liver 99% (1% unchanged via kidneys)
  - CYP 2D6 and 3A4
  - Monoethylglycinexilidide (MEGX)
    - Active metabolite
    - Additive to CNS side effects

Bupivacaine

- pKa 8.1
  - Slow onset of action
- Very potent
- Highly lipid soluble
  - Long duration of action
- CVS toxicity
  - Refractory ventricular fibrillation

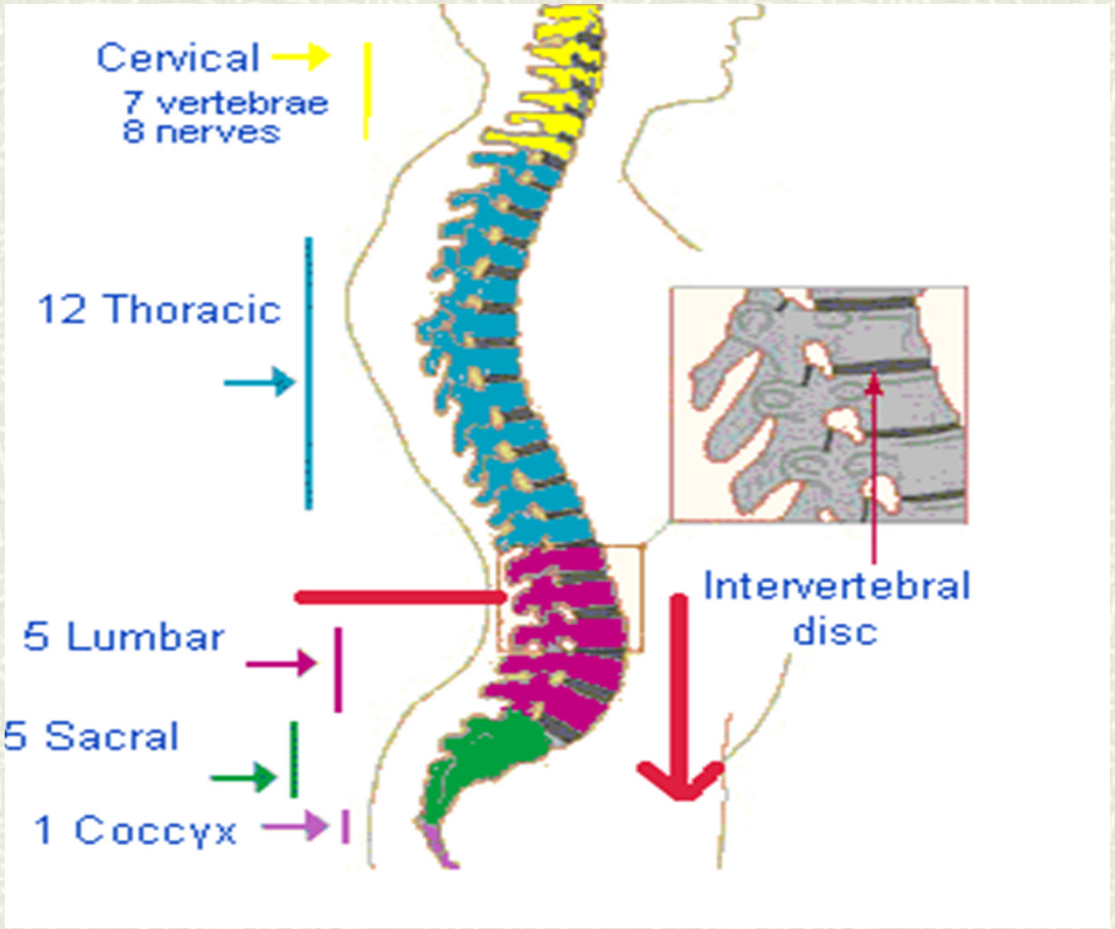
Lignocaine vs. bupivacaine

Drug	Lignocaine	Bupivacaine
Potency	4	16
Onset	Short	Prolonged
Duration	Short	Prolonged
Protein binding	64%	95%
Toxicity manifesting:	CNS	CVS

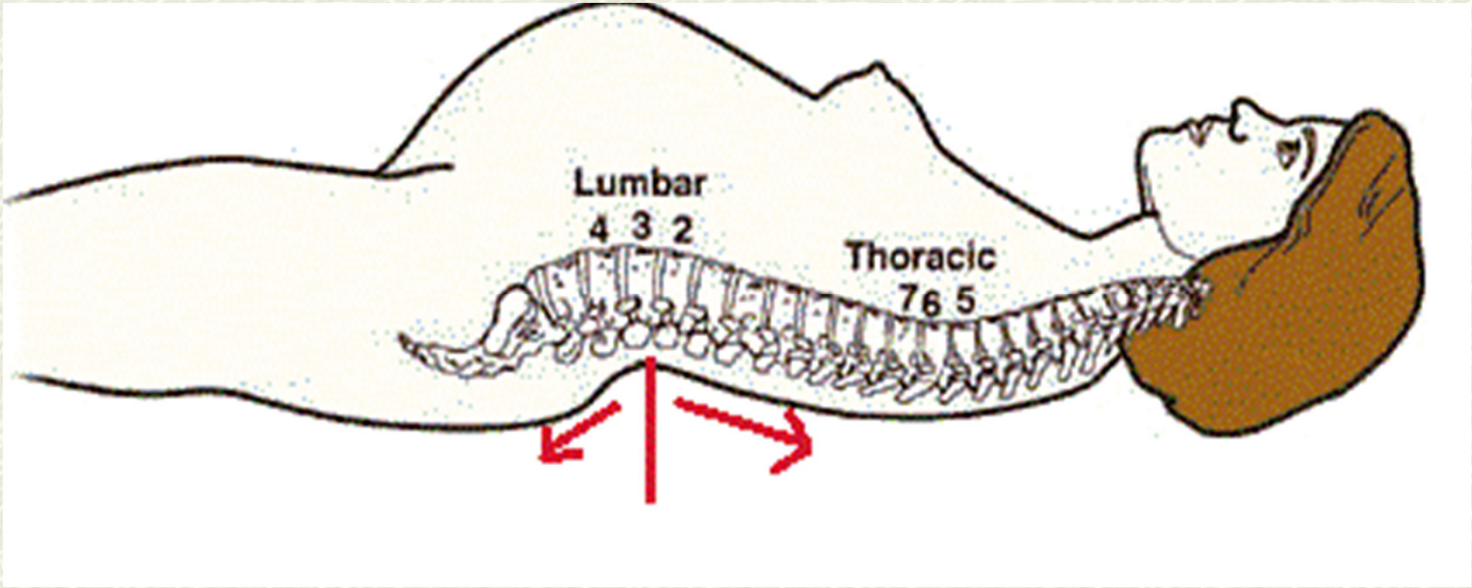
Additives to bupivacaine

- Glucose
  - 80mg (8%) added to “spinal bupivacaine”
- Increase the baricity of bupivacaine
- Heavier than CSF
- Gravitates to lower spinal regions
- Smaller dose for denser block.

Spinal anaesthesia: Heavy bupivacaine



Spread of “heavy” bupivacaine



Additives to local anaesthetics

- Vasoconstrictor = Adrenaline
  - Decreased absorption
  - Increased safe dose
  - Increased duration of action
- Opioids = morphine, fentanyl, sufentanil
  - Neuraxial = morphine vs fentanyl.
  - Increased duration of action.

Additives to local anaesthetics

- Alkalinize = $NaHCO_3$
  - Increased non-ionized fraction
  - **Faster onset of action**
  - Precipitation of adrenaline – no premix!!!
- Anticholinergics = Neostigmine
- A_2 agonists = clonidine, dexmedetomidine
  - Denser sensory blockade
  - Prolonged duration of action

Dosage

- Lignocaine = 1%
- ↓
- 1g in 100ml
- ↓
- 1000mg in 100ml
- ↓
- 10 mg/ml

- Bupivacaine = 0.5%
- ↓
- 0.5g in 100ml
- ↓
- 500mg in 100ml
- ↓
- 5mg/ml

Maximum dose for **infiltration**

- Lignocaine
  - 3-4mg/kg without adrenaline
  - 7mg with adrenaline
- Bupivacaine / L-bupivacaine
  - 2mg/kg irrespective of adrenaline
  - Maximum of 150mg
- Ropivacaine
  - 2mg/kg irrespective of adrenaline

Dosage calculation

- Child of **20kg** for suture laceration. How many **mls** of 2% lignocaine with adrenaline may he receive?
- Toxic dose with adrenaline = **7mg/kg**
- Total dose - 20kg x 7mg/kg **= 140mg**
- Each 2% vial has 20mg/ml of lignocaine
- Therefore – 140mg / 20 mg/ml =
  - **7ml of 2%**

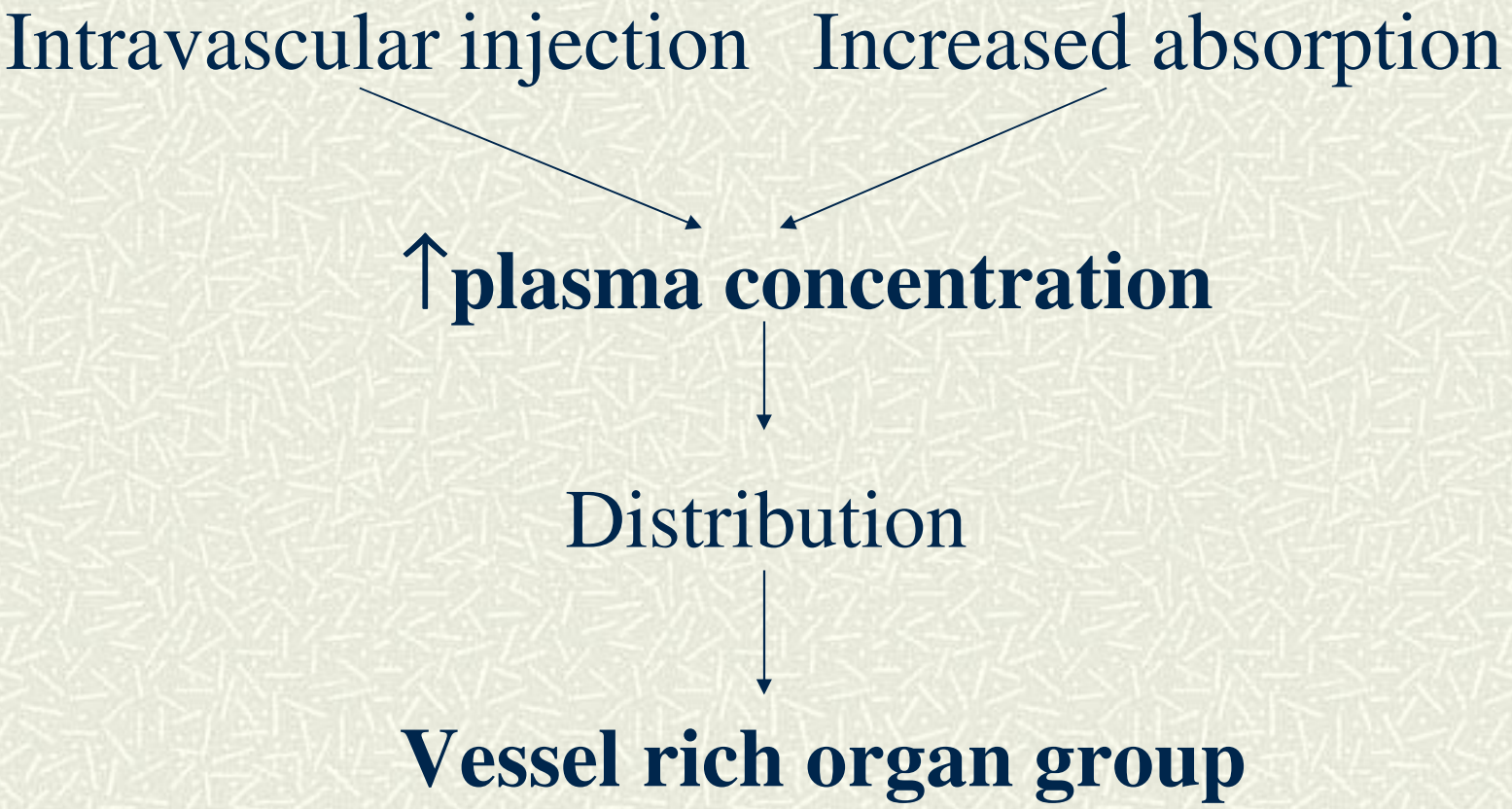
Dosage calculation

- Child of **20kg** for suture laceration. How many **mls** of **0,5% bupivacaine with adrenaline** may he receive?
- Toxic dose with adrenaline = **2mg/kg**
- Total dose - 20kg x 2mg/kg **= 40mg**
- Each 0,5% vial has 5mg/ml of bupivacaine
- Therefore – 40mg / 5 mg/ml =
  - **8ml of 0,5% bupivacaine!**

Toxicity: Classification

- Local toxicity
  - Neurotoxicity
  - Transient neurological symptoms
- Myotoxicity
- Systemic toxicity
  - CNS
  - CVS

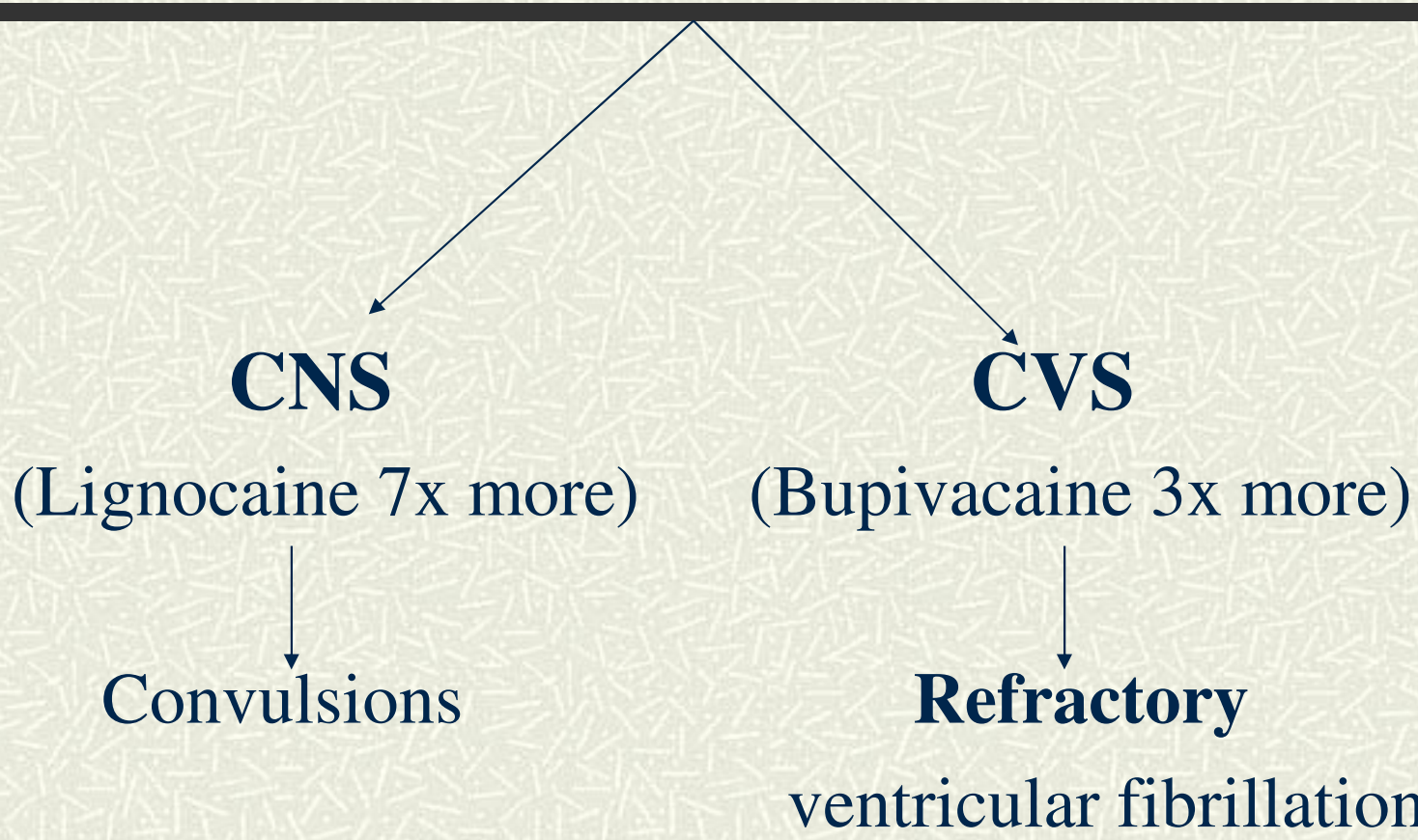
Systemic toxicity



Toxicity: ↑ absorption

- Excessive dose
- Site of injection
  - Intercostal>caudal>epidural>brachial plexus
- Physico-chemical properties
  - ↓ Lipid solubility }
  - ↓ Protein binding } ↑ absorption
  - ↓ Potency }
- Vasoconstrictor

Toxicity


CNS
(Lignocaine 7x more)
Convulsions
CVS
(Bupivacaine 3x more)
Refractory
ventricular fibrillation

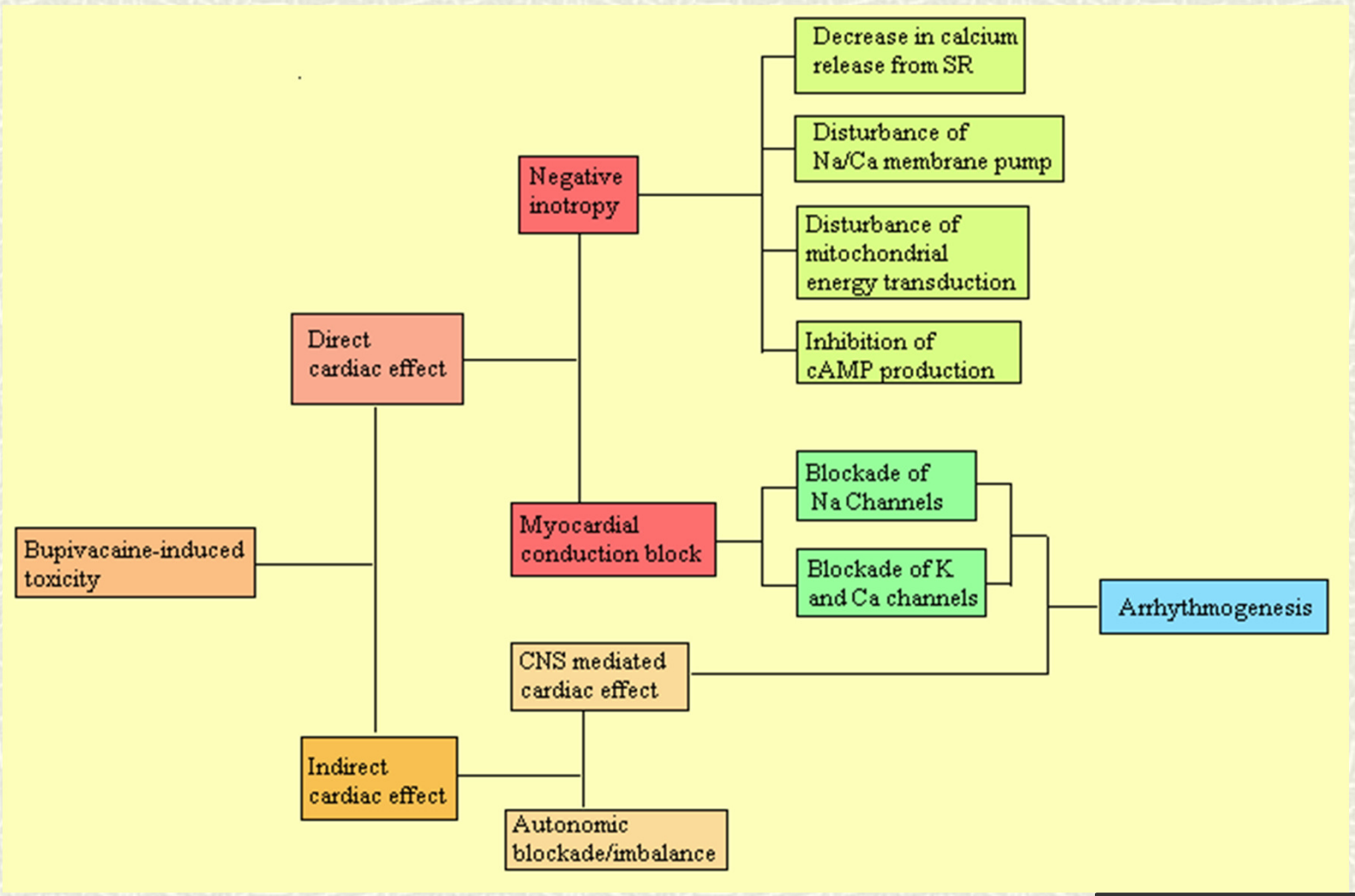
CNS toxicity

- Initial phase
  - Circumoral paresthesia, tinnitis, confusion
- Excitatory phase
  - Convulsions
- Depressive phase
  - Los of consciousness
  - Coma
  - Respiratory arrest

CVS toxicity

- Initial phase
  - Hypertension, tachycardia
- Intermediate phase
  - Myocardial depression → CO
  - Hypotension
- Terminal phase
  - Vasodilatation, hypotension, bradycardia
  - Conduction defects, dysrhythmias

Bupivacaine cardiac toxicity



Toxicity

- To ↓ complications due to bupivacaine

- Ropivacaine
- Levo-bupivacaine

Ropivacaine

- Amide , pKa = 8.1
- Lower lipid solubility
- Metabolism
  - Liver 99% (1% unchanged via kidneys)
  - CYP 1A2 (fluvoxamine ↓ metabolism 16%)

Ropivacaine

- Biphasic vascular effect
  - Low[ ] = vasoconstriction
  - High [ ] = vasodilatation
- Faster dissociation from cardiac Na^+ channels than bupivacaine
- Higher threshold for CNS symptoms

Ropivacaine: clinical uses

- Pain relief:
  - Epidural for labour, post op: **0.2%** @6-15ml/h
  - Surgery: **0.75%-1%** up to 12ml bolus
- Well differentiated block
  - Good sensory blockade
  - Much less motor blockade

L-bupivacaine

- L isomer of bupivacaine
- pKa 8.1
- As potent as racemic mixture
- Potentially less CVS toxicity
  - L-isomer less direct cardiotoxic effects

Rx of toxicity

- Convulsions
  - BZ
  - Thiopentone
  - Propofol
- Ventricular fibrilation
  - Bretilium
  - Intralipid®
  - K^+ channel openers

Rx of toxicity

- Ventricular fibrilation
  - Bretilium
  - Intralipid®
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Bretilium tosylate

- Class III anti arrhythmic
  - Slows phase 3 repolarisation
  - Prolongs refractory period
- ↓ release of NA
- Not manufactured currently

K^+ channel openers

- Pinacidil, bimakalim
  - Opens K^+_{ATP} channels
  - Shorten action potential in Purkinje fibers
  - Prolongs plateau phase
  - Hyperpolarise resting membrane potential

K^+ channel openers: side effects

- Shorten action potential =↓ Ca^{++} influx
  - Reduced contractility
- Excessive coronary vasodilatation
  - Coronary steal with steal prone anatomy

K^+ channel openers

- Improve AV conduction
- **But**
- Myocardial depression

Intralipid®

- Lipid emulsion
  - Soya oil
  - Egg phospholipids
  - Glycerol
- TPN, Propofol
- ↑ effective antidote
  - Bupivacaine induced CVS collapse

Intralipid® : proposed actions

- Lipid sink
  - Draws Bupivacaine from plasma
  - Decreased free fraction
- High lipid concentration
  - Forced lipid influx into myocyte
  - Overwhelms L-CAT
  - ↑ FFA for energy production
  - ↑ susceptibility for resuscitation