LOCAL ANESTHETICS

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LECTURE OUTLINE

❑ Mechanism of action

❑ Structure-activity relationship

❑ Pharmacokinetics of the drugs

❑ Clinical use

❑ Forms of local anesthesia

❑ Adverse effects

Local anesthetics (LAs)

- **Effect:** Reversible inhibition of neural activity by blocking the voltage dependent Na^+-channels of the neural axons.

- Consequence: Inhibition of the action potential formation.

Injected solution   Buffer tissue

$$-NH^+Cl^- + NaHCO_3 \longrightarrow -N + NaCl + H_2CO_3$$
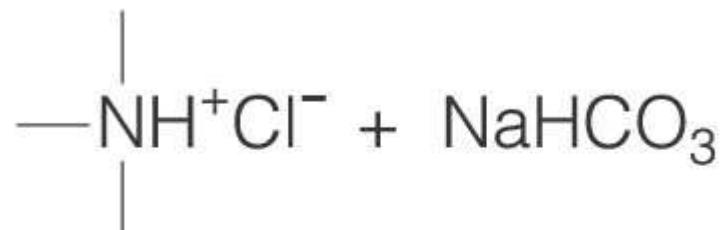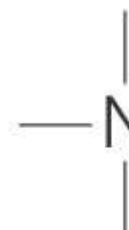
Water soluble   Lipid soluble
(Ionized form)   (Nonionized form)

pH= 4-6   pH= 7.3

MECHANISM OF ACTION

Rest

Activated

Inactivated

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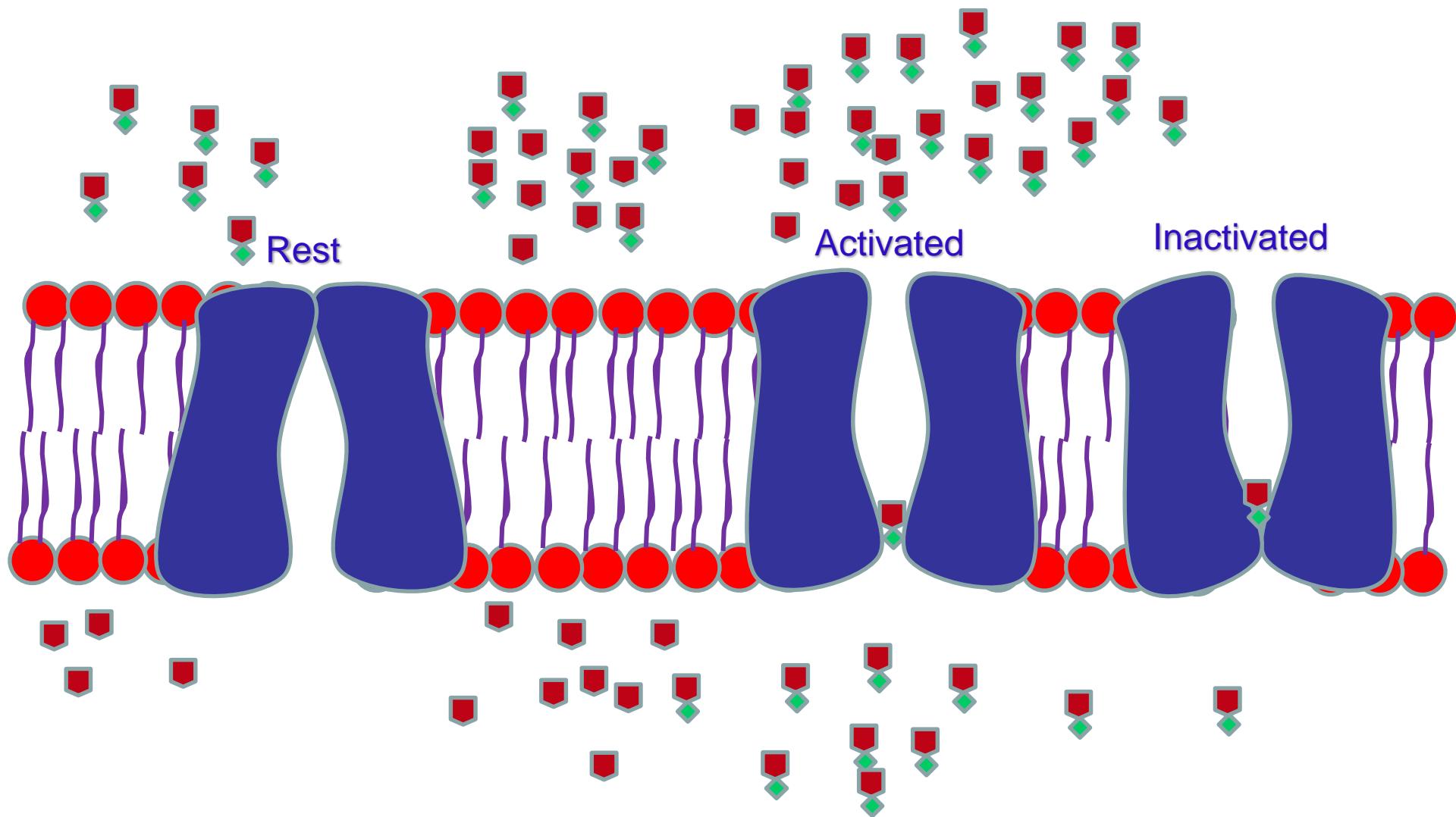
Frequency-dependent blockade:

LAs affect depolarized nerves (sensory, Aδ and C) more than less firing fibers (motor).

Differential blockade

The rank order of blockade:

sympathetic nerve (no myelin, C fibers), temperature, pain to pinprick, light touch, deep pressure and motor function (Larger nerves).

RELATIVE SIZE AND SUSCEPTIBILITY OF NERVE FIBER TYPES TO LAs BLOCKADE

| Fiber Type	Function	Diameter (µM)	Myelination	Conduction Velocity (m/s)	Sensitivity to Block
Type Aα	Proprioception, motor	12-20	Heavy	70-120	+
Type Aβ	touch, pressure	5-12	Heavy	30-70	+ +
Type Aγ	Muscle spindles	3-6	Heavy	15-30	+ +
Type Aδ	Pain, temperature	2-5	Heavy	12-30	+ + +
Type B	Preganglionic autonomic	< 3	Light	3-15	+ + + +
Type C Dorsal root	Pain	0.4 -1.2	None	0.5-2.3	+ + + +
Type C Sympathetic	Postganglionic	0.3-1.3	None	0.7-2.3	+ + + +

Historical back ground

- 1860: cocaine synthesis (Niemann)
- 1879: cocaine as LA (Anrep)
- 1884: Carl Koller – Followed the advice of Sigmund Freud, and demonstrated its anaesthetic effect on the cornea
- 1905: Procaine (Einhorn)
- 1948: Lidocaine (Löfgren & Lundqvist)
- 1957 Mepivacaine
- 1963 Bupivacaine (Marcaine)
- 1972 Etidocaine……....

Erythroxylum coca Lam.
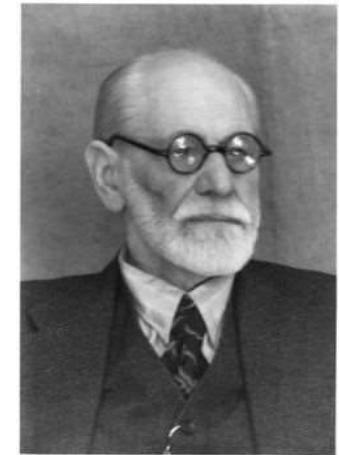
The chemical structure of local anesthetics

Cocaine

CH$_3$

COOCH$_3$

N

H

H

O — C

O
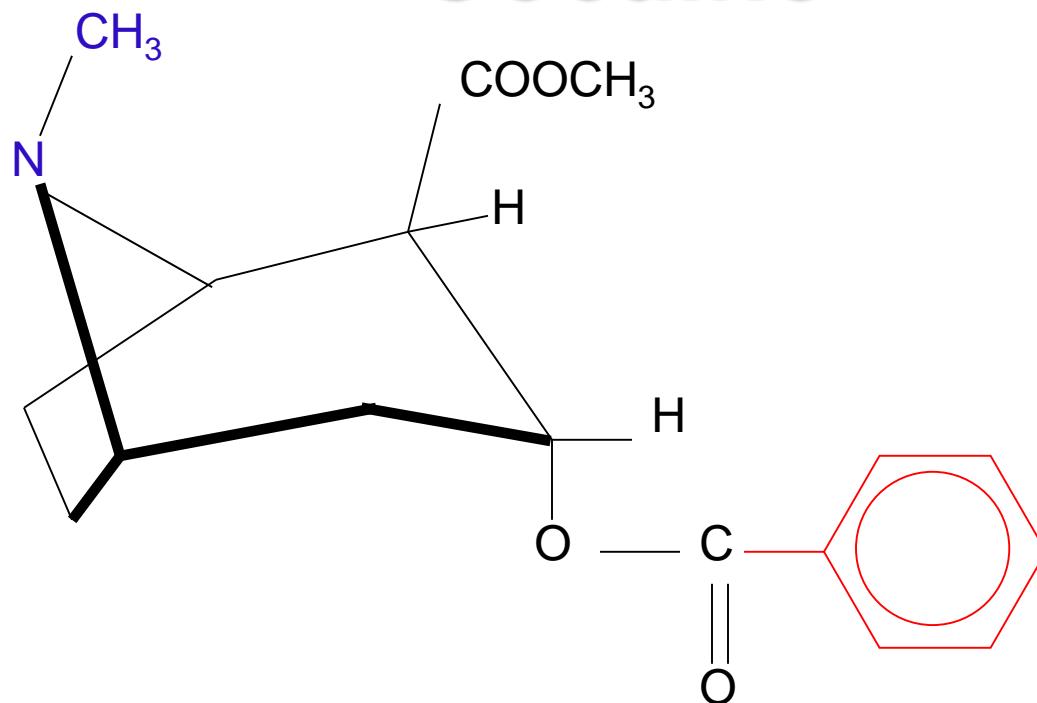
Amine (hydrophilic)

Intermediate chain

Aromatic group (lipophilic)

- For first time in 1884 were used in eye surgery (cocaine), topical application.

The chemical structure of local anesthetics

Aromatic part
Lipophilic

Intermediate chain

Amine part
Ionizable

$C-O - R_1$

Ester group

N R_1 R_3

$NH - C - R_1$

Amide group

N R_1 R_3

Intermediate chain
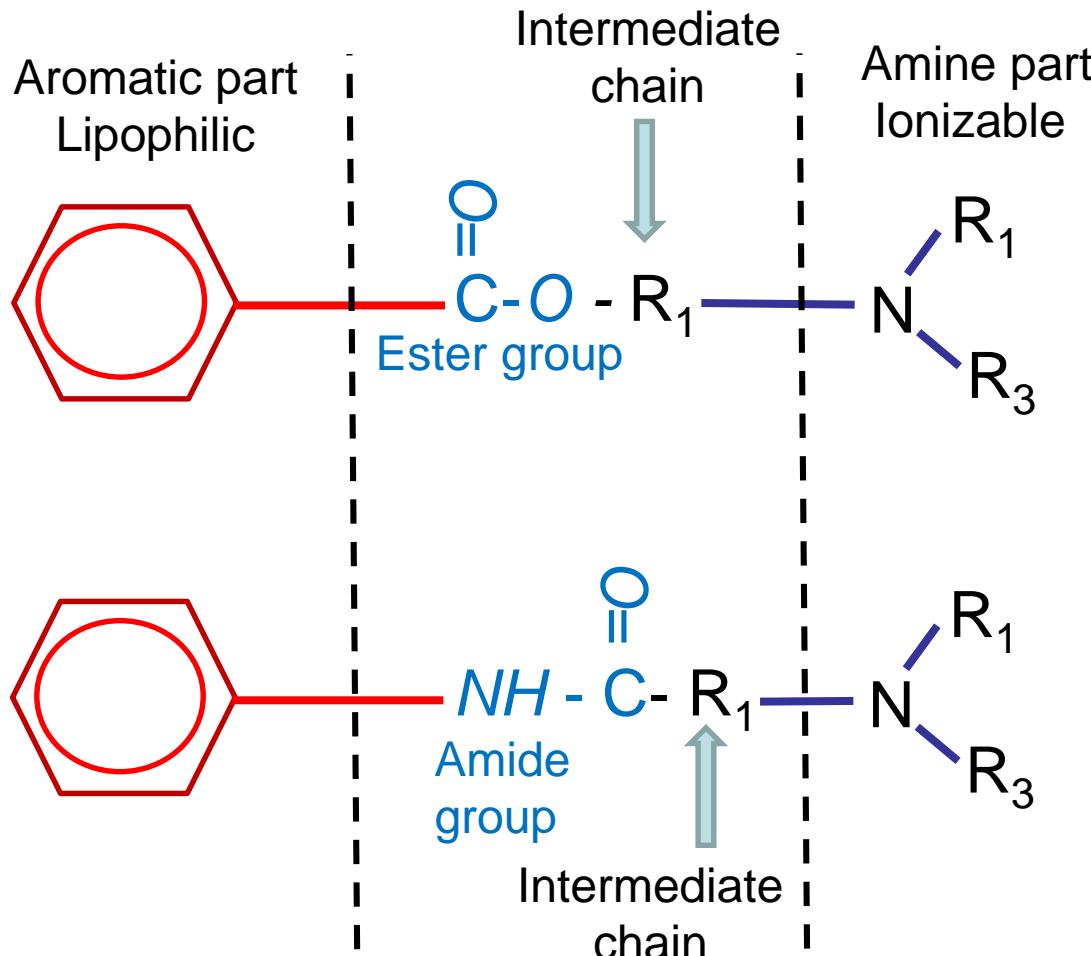
The classification of local anesthetics is based on the intermediate bonds

Factors affect the potency of local anesthetics

LAs action depends on:

- Environmental factors, the tissue's acid-base balance

(H⁺ concentration)

- Size of nerve, the presence and amount of myelin, and the

location of particular fibers within a nerve bundle, <u>the outer

fibers will be affected first</u>. Frequency of nerve stimulation.

- Factors affect the rate of LAs uptake by vessels

(Vasodilator/vasoconstrictor profiles)

- Electrolyte concentrations

Ester local anaesthetics

	pKa	Speed on set	Potency procaine=1	Duration of action
Benzocaine	**3.5**	surface		
Proca**i**ne	**9**	slow	1	Short (6min)
Coca**i**ne	**8.7**	slow	2	medium
2-chloroproca**i**ne	**9.3**	rapid	2	medium
Tetraca**i**ne	**8.6**	slow	16	long

Other analogs:
Pramoxine
Dyclonine
only for surface anesthesia

pKa = pH at which ionized form local anesthetic = non-ionized form

Amide local anaesthetics

	pKa	Speed of set	Potency procaine=1	Duration of action
Lidocaine	7.7	fast	4	medium
Mepivacaine	7.9	fast	2	medium
Bupivacaine	8.1	slow	16	Long*
Levobupivacaine	8.1	slow	14	Long #
Ropivacaine	8.1	slow	10	Long#
Etidocaine	7.9	fast	16	Long+, *
Articaine Thiophene ring+ ester	7.8	fast	10	medium
Prilocaine	7.9	fast	3	Medium**

*Cardiotoxic, + motor blockade, # less cardiotoxicity than Bupivacaine

** Methemoglobinai

-Water solubility high

- High binding to proteins

LIDOCAIN pKa = 7.7

Human tissue
PH=7.4

pH = pK + log [base]/[salt]

Lidocaine 7.7
Inflamed tissue
PH=6.7
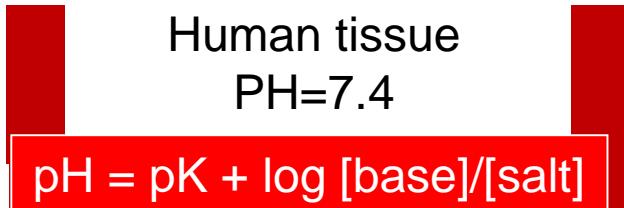
$7.4 - 7.7 = -0.3$ ⬅ Log

$6.7 - 7.7 = -1$ ⬅ Log

[nonionized]/[ionized] = 0.5

$\approx 1:2$ ➡ **ionized**
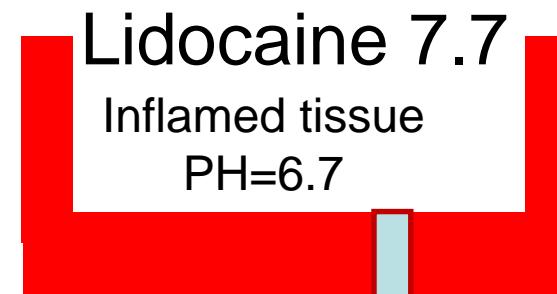
0.1=1/10

$\approx 10:1$ ➡ **Non Ionized**

NONIONIZED

IONIZED

1 work : 2 not work

☺

1 work : 10 not work

☺

TETRACAIN pKa = 8.6

Human tissue PH=7.4

$pH = pK + \log [base]/[salt]$

$7.4 - 8.6 = -1.2$ ⟵ Log

$[nonionized]/[ionized] = 6/100$

$\approx 6:100$ ⟹ **ionized**

NONIONIZED

Henderson-Hasselbalch equation

$pH = pK + \log [base]/[salt]$

$pH = pK + \log [nonionized]/[ionized]$

$7.4 = 8.6 + \log [nonionized]/[ionized]$

$-1.2 = \log [nonionized]/[ionized]$

$6*10^{-2} = [nonionized]/[ionized]$

$6/100 = [nonionized]/[ionized]$

$6:100 = [nonionized]:[ionized]$

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LAs of small pKa (base) have a more rapid onset of action

Pharmacokinetics

Uptake	Distribution	Elimination
	lipid solubility & protein binding	Metabolism & excretion
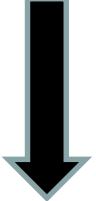
Absorption & site of injection (based on the vascularity of area)

↓ Adrenalin (0.001 %). (1:100000)

VASOCONSTRICTORS

Advantages:
- ↓ the access of LAs to the circulation
- ↑ the duration of LAs
- ↓ the amount of LAs needed for nerve blockade
- ↓ the blood loss during surgical intervention.

Pharmacokinetics

Elimination

Metabolism & excretion

Metabolism:

- Ester analogs

 Plasma pseudocholinesterase (except cocaine).

 Atypical plasma cholinestrase (reduction or absent).

Nonspecific esterases, cocaine slow metabolism (liver).

Procaine metabolismusm

H_2N — (benzene ring) — C — O — CH_2 — CH_2 — N — C_2H_5 / C_2H_5

‖
O

+

H_2O

pseudocholinesterase

OH
|
H_2N — (benzene ring) — C
‖
O

HO — CH_2 — CH_2 — N — C_2H_5 / C_2H_5

p-aminobenzoic acid   diethylamino-ethanol
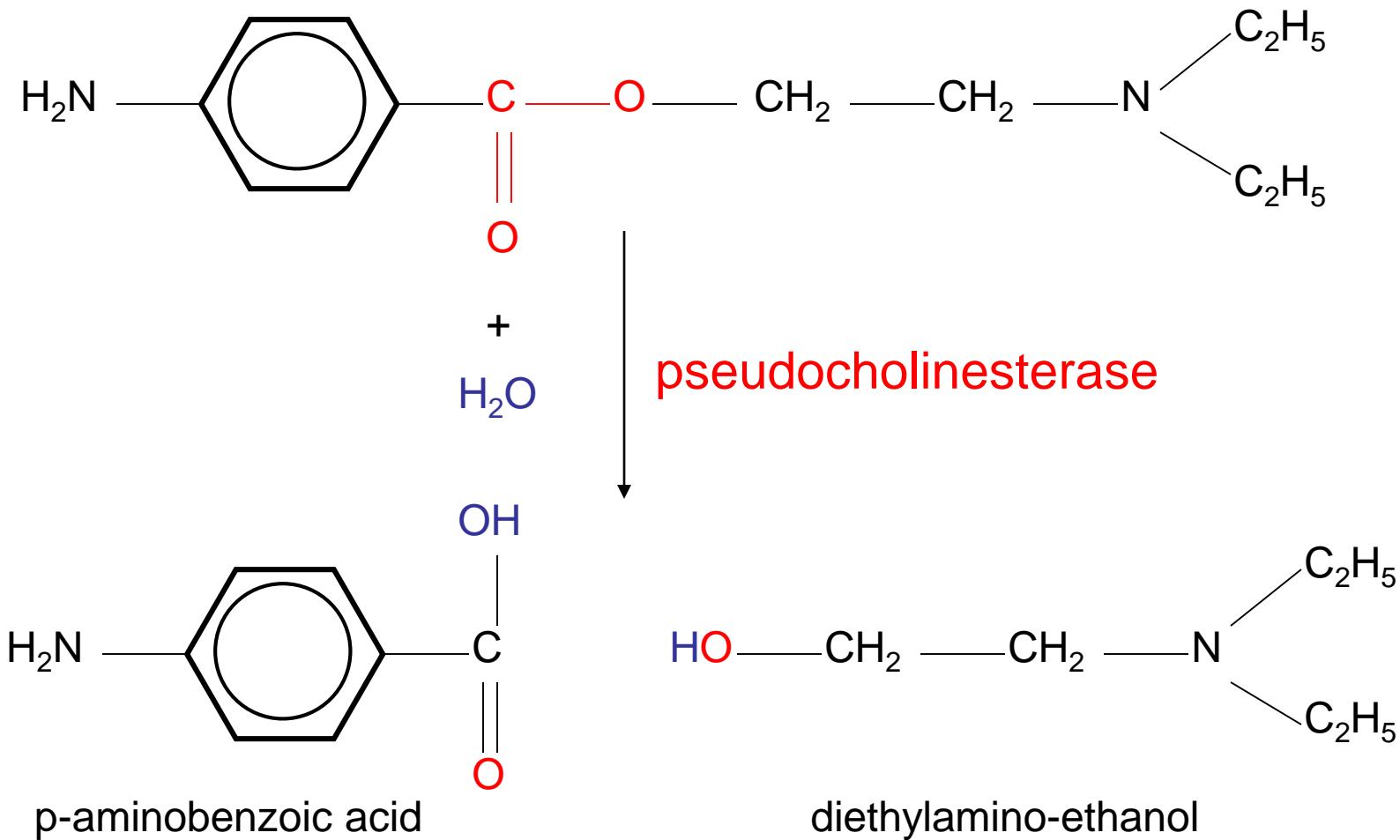
Pharmacokinetics (Metabolism)

- Amide analogs:

 P450 isoenzymes: hydroxylation, N-dealkylation,

Methylation $\rightarrow$ more water soluble metabolites $\rightarrow$ kidney.

The rank of metabolism: prilocaine > lidocaine >

mepivacaine > ropivacaine = bupivacaine > levobupivacain.

Fast: etidocaine, prilocaine

Intermediate: lidocaine, mepivacain

Slow: ropivacaine, bupivacain

Elimination by kidney is accelerated by acidification

of tertiary amine compounds.

Forms Of Administration

- Topical use (Infiltration, perineural).

- Regional Block

- Spinal Anesthesia

- Lumbar Epidural Anesthesia

- Caudal Anesthesia

- Intravenous Extremity Block

- Sympathetic Block

Clinical Use

- Dental, Ophthalmology, throat, urologic interventions

- Obstetrics

- Painful diagnostic procedures

Form of anesthesia	Site of effect	Indication	Drug
Surface	Nerve endings of skin, mucous membranes	Dentistry Surgery Diagnostics Ophthalmology Dermatology	Tetracaine Lidocaine Prilocaine Proparacaine Dibucaine Pramoxine
Infiltration	Subcutanous nerve endings	Dentistry Surgery	Lidocaine Bupivacaine Articaine *procaine
Conduction (regional)	Mixed nerve	Dentistry	Lidocaine Bupivacaine Articaine Mepivacaine Prilocaine *procaine

* Is poorly absorbed from the mucous membranes

Form of anesthesia	Site of effect	Indication	Drug
Spinal	Spinal roots	Gynecology Urology Surgery	Lidocaine Bupivacaine Articaine Prilocaine Chloroprocaine
Epidural	Epidural space		

	Procaine		Lidocaine			Tetracaine
	infiltration	regional	infilt.	regional	surface	surface
Concentration (%)	0.5	1-4	0.5	1-2	2-4	1-2
Maximal total dose (mg)	500 1000		300 500		200	20
Onset of effect (min)	5-10		<2		<2	10
Duration of effect (min)	<40 >60		60-90 180-240			180-240
Red print: in the presence of a local vasoconstrictor Blue print: without local vasoconstrictor						

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| Drug	Potency		Toxicity	Elemination rate	
	Surface	Conduction		Hydrolysis	Liver
Procaine	1	1	1	1	
Mepivacaine	4	2	1		1
Lidocaine	4	2	1.5		0.5
Cocaine	20	4	4	0.15	
Tetracaine	400	25	30	0.08	

Adverse effects

- CNS effects:
  - dizziness
  - vomiting
  - anxiety
  - epileptiform convulsions
  - coma, death
- Cardiovascular system:
  - (-) chronotropic effect
  - AV-block
  - bradycardia
  - cardiac arrest
  - vasodilation

- Cocaine:
  - vasoconstrictor by itself
  - psychostimulant
    - cortical activity ↑
    - mental performance ↑
    - social activity ↑
    - ↓ tiredness
- All these effects are due to the blockade of NE re-uptake

Allergy - mostly the esthers

Avoid their combination because main and toxic effects can be predicted

Daniel E Becker et al., 2012
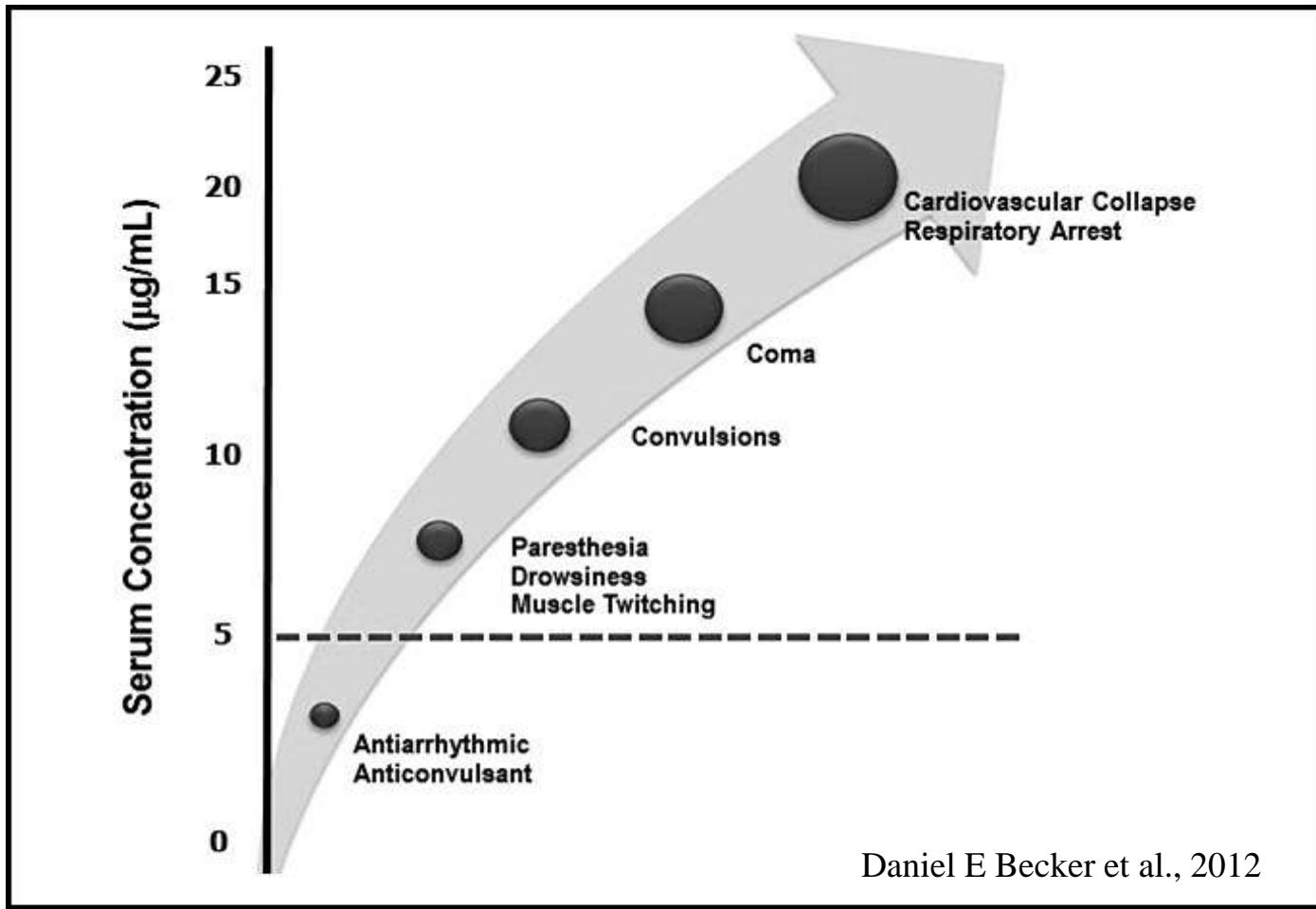
Lidocaine effect vs serum concentration

Pharmacodymamic interactions with LAs

Nearly all LAs	MAO inhibitors	cardiovascular alterations
	tricyclic antidepressants	cardiovascular alterations (due to the action of CA)
	antiarrythmic drugs	cardiac rhythm disturbances
	alcohol	respiration depression
	skeletal muscle relaxants	increase in the action of LAs
Lidocaine	antiepileptic drugs	increase in the cardiac and central nervous system adverse effects

Pharmacokinetic interactions with LAs

Nearly all LAs	anticoagulants, NSAID	Bleeding (due to changing of the metabolism)
Procaine	sulfonamides	the effect of S $\downarrow$
Amide-linked LAs	cancer, MI, uremia	Binding to plasma protein
	trauma, smoking	
	oral contraceptives	
	neonatal patient	deficiency of plasma protein
Ropivacaine	alfentanil, midazolam	metabolism of R decreased
	fluvoxamine, verapamil	
	theophylline, ketoconazol	
Lidocaine	halothane, propranolol	metabolism of L decreased

LOCAL ANESTHETICS

The ideal local anesthetic

- Has low systemic toxicity when applied in effective conc.

- Fast onset, reasonble duration of action.

- Good water solublilty and stablity in the solution.

- Stable when sterilizid by heat.

- Can be used for tissue and surface

      (mucous, membranes) anesthesia.

- It's action is reversible.

Thank you for your attention