LOCAL ANESTHETICS

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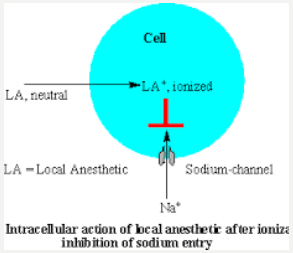
LEARNING OBJECTIVES

- Mechanism and Termination of Action
- Types of Local Anesthetics
- Allergic Potential
- Dosage Limits
- Local Anesthesia Systemic Toxicity (LAST)

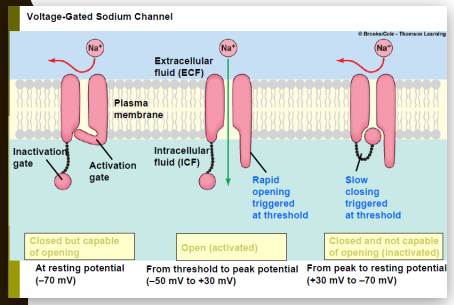
MECHANISM OF ACTION

- Injected local anesthetic rapidly dissociates into an uncharged base (LA) and an ionized conjugate acid (LA+)
- The base (uncharged portion) can pass through the lipid membrane.
- Reversibly binds to the alpha subunit of voltage gated sodium channel



Intracellular action of local anesthetic after ioniz
inhibition of sodium entry

NA+ CHANNEL INACTIVATION



- Once inside the cell it becomes ionized. This LA+ (acid) binds to the alpha-subunit on the inside of the voltage gated sodium channels
- It effectively "plugs" the channel so the Na+ cannot pass therefore blocking nerve conduction process
- The channel is in a closed inactive state once the local binds. In this state the channel cannot be opened

ACTION & CHARACTERISTICS OF LOCAL ANESTHETICS

- Onset of action
  - pKa value
  - Concentration of drug (dose administered)
- Potency
  - Lipid solubility
- Duration of action
  - Protein binding
  - Vasoconstrictor added?

HENDERSOHN-HASSELBACH EQUATION

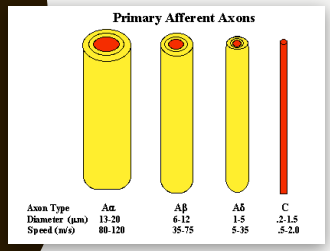
$pH = pK_a + \log K_a$

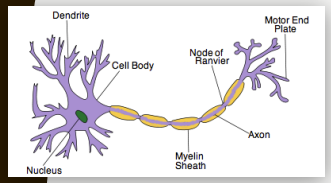
At the midpoint, $K_a = 1$ and $pH = pK_a$

The pH at the midpoint is equal to the pK_a

DIFFERENTIAL SENSORY AND MOTOR BLOCKADE

- Local anesthetics ability to affect the nerve
  - Bupivacaine good example sensory blockade with minimal motor until high dose
- Anatomy of the nerve axon
- Nerves sensitivity behavior



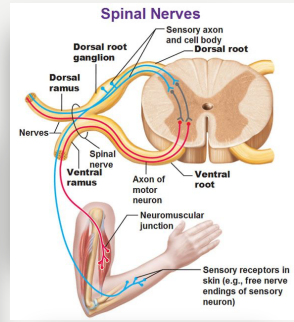


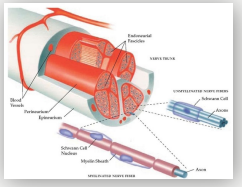
NERVE FIBER REVIEW

- Peripheral nerves can vary in
  - Size
    - Wider diameter nerves conduct signal faster than narrow ones
  - Presence of myelin (myelination)
    - Insulates the nerve, faster conduction of signal
  - Structure

NERVE FIBER REVIEW

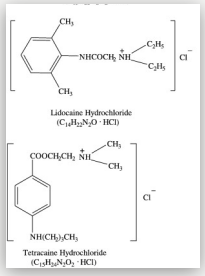
Fiber type	Function	Diameter (mm)	Conduction (m/s)	Myelinated
Aα	Motor efferent	12-20	70-120	yes
Aα	Proprioception	12-20	70-120	yes
Aβ	Touch, pressure	5-12	30-70	yes
Aγ	Motor efferent	3-6	15-30	yes
Aδ	Pain, temp, touch	2-5	12-30	yes
B	Paraganglion autonomic	<3	3-14	some
C dorsal root	Pain, temperature	0.4-0.12	0.5-2	No
C sympathetic	Postganglionic sympathetic	0.3-1.3	0.7-2.3	No





CHEMICAL STRUCTURE OF LOCAL ANESTHETICS

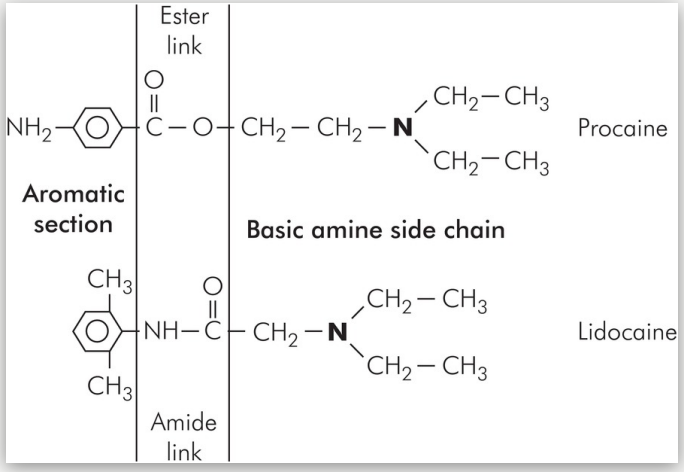
- The typical local anesthetic molecule contains a tertiary amine attached to a substituted aromatic ring by an intermediate chain that contains either ester or an amide linkage
  - Aromatic ring gives a lipophilic character
  - Tertiary amine end is relatively hydrophilic
  - LA is classified as amino-ester or amino-amide compounds



TYPES

Amides

Esters



ESTERS

- Metabolized by Pseudocholinesterase
  - *Cocaine also metabolized in the liver
    - Benzocaine
    - Cocaine
    - Chloroprocaine
    - Procaine
    - Tetracaine

Generic Name	Trade name	Duration of action	Unique characteristics
Benzocaine*	Americaine	SHORT	Only Weak base No ionization Met-Hb
Cocaine*		1-hour plasma half life	* metabolized in liver also. vasoconstrictor!
Chloroprocaine	Nesacaine	SHORT	Least toxic of LA
Procaine		SHORT	Poor protein binding, low toxicity
Tetracaine*	Pontocaine	LONG	93% ionized at 7.4 76%protein binding

ESTERS

AMIDES

Amide- has "I" before -caine

Bupivacaine	Dibucaine	Etidocaine	Lidocaine	Mepivacaine	Ropivacaine

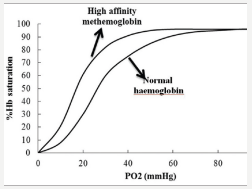
- Amides are metabolized in the liver by CYTP450

Name	Trade name	Duration of action	Unique characteristics
Bupivacaine	Marcaine	LONG	96% protein binding
Dibucaine	Nupercaine	LONG	
Etidocaine	Duranest	LONG	Highly protein bound
Lidocaine*	Xylocaine	MODERATE	*neurotoxicity in sab
Mepivacaine*	Carbocaine	MODERATE	75% protein binding
Prilocaine*	Citanest	MODERATE	55% protein binding
Ropivacaine	Naropin	LONG	94% protein binding

AMIDES

METHEMOGLOBINEMIA

- Methemoglobin (MetHb) is altered state of hemoglobin (Hb)
  - Ferrous (Fe2+) irons of heme are oxidized to the ferric (Fe3+) state
  - Results in *left shift* of oxygen dissociation curve,
    - Less o2 released at tissue
- *Signs: cyanosis and low spo2 with normal arterial PO2 on ABG, chocolate colored blood, brown urine*



METHEMOGLOBINEMIA

- Congenital or Acquired
  - Specific medications can cause oxidation of Hb to MetHb
    - Local anesthetics
      - Prilocaine, lidocaine and benzocaine*
    - Anesthesia adjuncts
      - NTG, phenytoin, sulfonamides, metoclopramide, nitrous oxide, chloroquine

METHEMOGLOBINEMIA TREATMENT

- **If asymptomatic with MetHb <20% no therapy necessary, just d/c causative agent**
- **Increase oxygen delivery to patient**
- **Administer Methylene blue**
- **Hyperbaric O2 and exchange transfusions alternate treatments**

METHYLENE BLUE

- Accelerates enzymatic reduction of methemoglobin
  - Converts ferric ion (fe3+) back to ferrous state (fe2+)
- Inhibitor of nitric oxide synthase and guanylate cyclase
  - Improves hypotension in septic shock
- Antimalarial

- Dosing for Methemoglobinemia
  - If >20% MetHgb administer 1-2mg/kg of 1% solution IV over 5 minutes.
  - Dose can be repeated in 30-60 minutes
  - Total dose should not exceed 7-8mg/kg

METHYLENE BLUE CONSIDERATIONS

- Contraindicated in pts with G6PD deficiency patients [causes hemolysis]
  - Alternative treatment: Ascorbic acid 2mg/kg or IV thionine
- Can be toxic if high dosage administered
  - Cardiac arrhythmias, coronary vasoconstriction, decreased CO, decreased renal blood flow ,increased pulmonary vascular pressure and resistance
  - Dose dependent toxic CNS effects: Confusion, h/a, dizziness or tremors
  - MAO inhibiting properties can precipitate fatal serotonin toxicity >5mg/kg
  - Anaphylaxis has been reported
- Rebound Methemoglobinemia can occur 18 hours after methylene blue administration
- *False depression in o2 sat reading with administration!

LOCAL ANESTHETICS AND ALLERGIC REACTIONS

ALLERGIC REACTIONS

ESTERS

- Low allergic potential
- Cross sensitivity possible between Esters

AMIDES

- Extremely rare to have an allergy to Amide Local Anesthetic
- No cross sensitivity within Amide class if allergy exists

There is *no cross sensitivity* between Ester and Amide classes

LA ALLERGY

- More common with Esters
- Ester type local anesthetics are derivatives of para-aminobenzoic acid (PABA)
- PABA is an immunogenic molecule (cross sensitivity within class)

UPTAKE AND TERMINATION OF ACTION

- Absorption into the systemic circulation removes the LA from the site of action (termination of effect)
- Higher amount of vascular uptake=Cp (plasma concentration)
- Influential factors for Vascular uptake and Cp
  - Site of injection
  - Tissue blood flow
  - Physiochemical properties of LA
  - Metabolism
  - Addition of vasoconstrictor

INJECTION SITE VASCULARITY

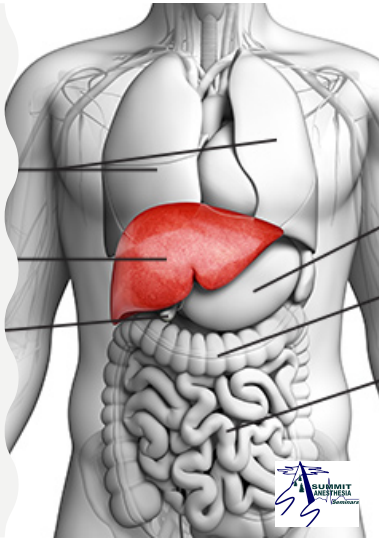
Interpleural
Intercostal
Caudal
Epidural
Brachial plexus
Femoral
Sciatic
Subcutaneous

Most Vascular

Least Vascular

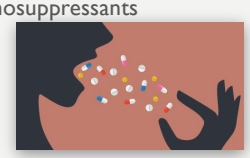
LA METABOLISM

- Factors that may decrease LA metabolism
  - –Amide local anesthetic is metabolized in the liver
- Predisposition to lidocaine toxicity directed r/t to decrease hepatic excretion
  - Decreased cardiac output
  - Cytochrome P450 inhibitors
    - –Specifically 3A4 and 1A2
  - Liver conditions (Cirrhosis)



CYTOCHROME P450 INHIBITORS

- Anesthetics
- Anti-Arrhythmia Drugs
- Antibiotics/Antifungal/Antiviral
- Anti-Depressants
- H2 blockers
- Anti-Neoplastic
- Immunosuppressants
- Anticonvulsants
- Antihypertensive/Cardiac
- Calcium channel blockers:
- Cholesterol medications:
- Steroids
- Herbs/Foods
- Other: Methadone, Thyroxine



LA PLASMA LEVEL FACTORS

- Injected tissue acts as reservoir for LA
- Plasma protein binding helps limit Cp
- Metabolism decreases Cp
- Vasoconstrictor use decreases systemic absorption

LIDOCAINE TOXICITY

PLASMA CONCENTRATION	TOXIC MANIFESTATIONS
3ug/ml	Circumoral and tongue numbness
4ug/ml	Lightheadedness and tinnitus
6ug/ml	Visual disturbances
8ug/ml	Muscular twitching
10ug/ml	Unconsciousness
12ug/ml	Convulsions
15ug/ml	Coma
20ug/ml	Respiratory Arrest
26ug/ml	Cardiovascular Collapse

LAST (LA SYSTEMIC TOXICITY)

Local injected

- Systemic absorption of local anesthetic r/t dosage, vascularity of injection site and vasoconstrictor in local solution

CNS symptoms

- Restlessness, tinnitus, circumoral numbness. Lightheadedness, visual disturbances
- Seizures, apnea

CV collapse

- Profound hypotension
- Possible myocardial depression r/t blockage of cardiac sodium channels

LAST TREATMENT RECOMMENDATIONS

- Circumoral numbness
- tinnitus

Observe patient/ Apply o2

Administer barb/benzo & get help

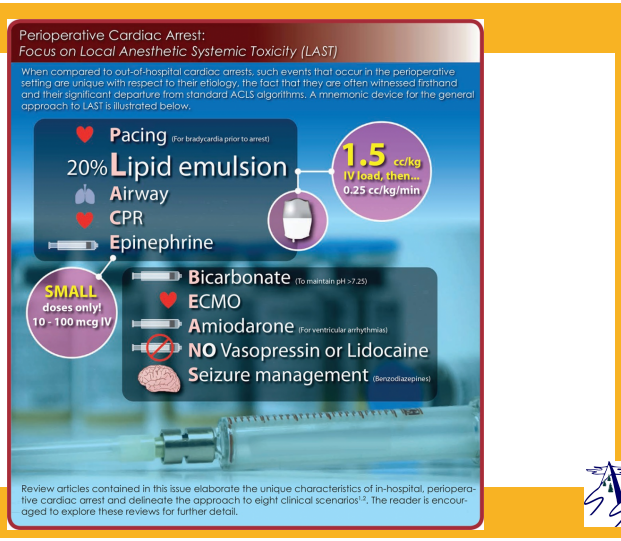
- lightheadedness
- Slurred speech
- Altered LOC

- Seizure activity
- Apnea

Hyperventilate, support airway

Monitor vs closely administer intralipids prn

- hypotension
- Cardiac changes



LIPID EMULSION

- Mechanism of action
  - Lipid sink
- Dosage
  - Bolus 20% 1.5ml/kg (lean body mass) over 1 minute
  - Infusion 0.25ml/kg/min
  - Maximum dose 10ml/kg in first 30 minutes

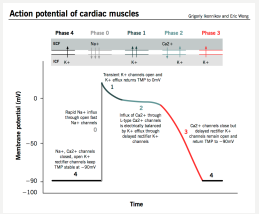
FACTORS THAT AFFECT LAST

- Increase risk of LAST
  - Hypercarbia
  - Hyperkalemia
  - Metabolic Acidosis
- Decrease risk of LAST
  - Hypocarbia
  - Hypokalemia
  - CNS depressants

CARDIAC TOXICITY

- Cardiac action potential, myocardial performance and vascular resistance are disrupted by LA

- Factors can determine the extent of cardiotoxicity
  - Affinity for voltage gated sodium channels
  - Rate of disassociation from the receptor



* Bupivacaine has a greater affinity for voltage gated sodium channel than lidocaine and a slower rate of dissociation.

MAXIMAL DOSAGES

Medication		Max dose (mg/kg)	Max total dose (mg)
Bupivacaine	plain w/ epi	2.5 3	175mg 200mg
Chloroprocaine	plain w/epi	11 14	800mg 1000mg
Lidocaine	plain w/epi	4.5 7	300mg 500mg*
Mepivacaine		7	400mg
Prilocaine		8	500mg *
Procaine		7	600mg
Ropivacaine		3	200mg

TUMESCENT SOLUTION

- Developed in 1980s.
- Tissue is swollen and firm = tumescent
- 1 L NSS with additives used to infiltrate subcutaneous tissue to allow for liposuction cannula extraction of excess fat

TUMESCENT SOLUTION COMPONENTS

- Lidocaine 0.05%-0.1% solution
  - Max dose lidocaine 35-55mg/kg in tumescent

- Epinephrine 0.5mg-1.0 mg per L fluid
  - Max epi dose 50mcg/kg

- Sodium Bicarbonate
  - 12.5 meq per L fluid

SAFE TUMESCENT DOSAGES

- 25ml of 2% lidocaine in 1L bag
  - What is concentration of solution? How many mg/ml?
  - 25 x 20mg/ml + 500mg in 1L bag=0.5mg/ml or 0.05% solution

- How much of above solution can a 70kg patient receive safely?
  - Safe dosage for lidocaine 35-55mg/kg in tumescent solution
  - 70x35mg/kg=2450mg if 0.5mg/ml= 2450x2= 4900ml solution
  - 70x55mg/kg=3850mg if 0.5mg/ml= 3850x2= 7700ml solution

EPINEPHRINE IN TUMESCENT SOLUTION

- Epi 1ml of 1:1000 equals 1mg/ml or 1000mcg diluted in 1000ml so 1mcg/ml
- Recommended safe dosage 50mcg/kg
  - 70kgx50mcg =3500mcg total =3500ml tumescent acceptable

SUMMARY

- Knowledgeable of:
  - Medication being administered
  - Appropriate dosage
  - Aware of allergic potential
  - Prepared for LAST

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Any Questions?

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