UCI University of California, Irvine

Local Anesthetics & Intralipid Therapy

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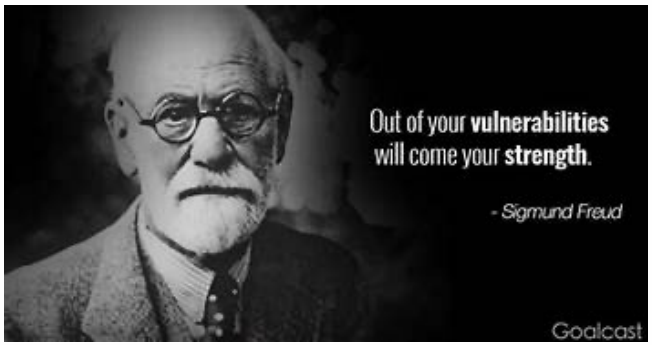
Disclosures

I do not have financial or nonfinancial interests to disclose



Learning Objectives: Following the lecture you should be able to…

1. Understand the pharmacology of local anesthetics agents.
2. Identity the properties of local anesthetics that determine the
    - classification
    - onset & duration of action
    - anesthetic potency
3. Learn about the benefits associated with regional anesthesia as an adjunct for postoperative pain management.
4. Determine the symptoms suggestive of local anesthetic systemic toxicity (L.A.S.T.).
5. Discover the role of intralipid therapy for the treatment of L.A.S.T.

History and Discovery

- Incas: Andes Mountains Coca leaves
- 1884 Dr. “Coca Koller” & Sigmund Freud
- 1891: Albert Niemann synthesized pure cocaine
- 1885: American Surgeon William Halstead injected 4% cocaine into sensory nerve trunk to create surgical anesthesia.

A. Nieman 1834-1861

K. Koller
1857-1944

C. Leake (L) 1896 - 1978

W. Halstead
1852-1922

"Modern" – Current Local Anesthetics

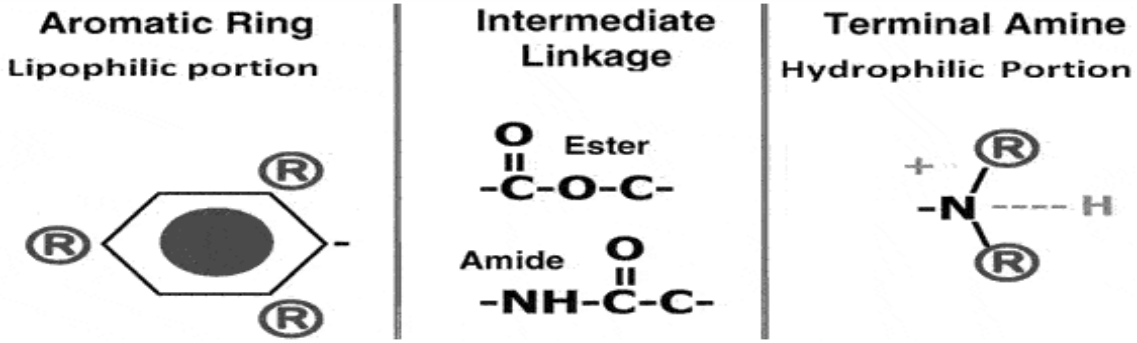
- 1891 – 1930: Synthesis of new Amino Esters: tropocaine, eucaine, holocaine, **benzocaine,** & **tetracaine**.
- 1898 – 1972: Amino Amides: nirvaquine, **procaine, chloroprocaine,** cinchocaine, **lidocaine, mepivacaine, prilocaine,** efocaine, **bupivacaine, etidocaine**, and articaine
- 1996: **Ropivacaine,** a pure S(-) enantiomer
- 2012: **Exparel,** Liposomal Bupivacaine

Chemistry of Local Anesthetics

A. Lipophilic aromatic ring: lipophilic base, enters the nerve membrane → *potency*

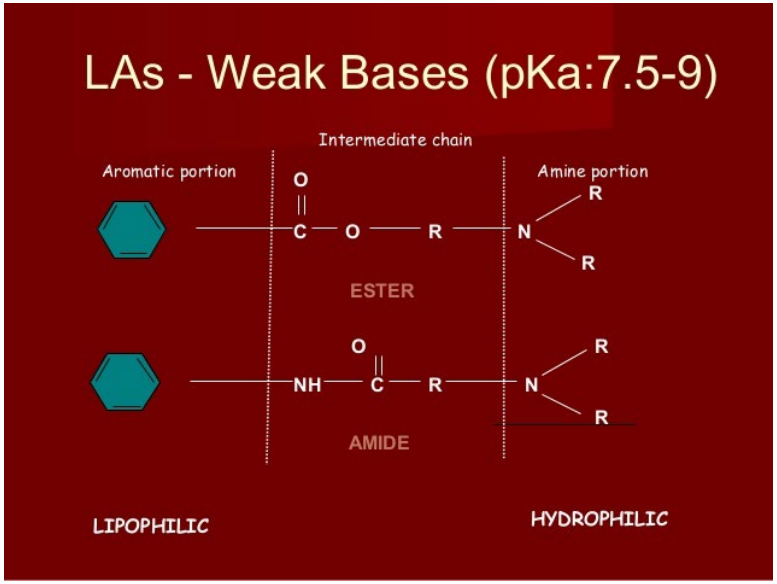
B. Amide chain or Ester: Intermediate chain determines class

C. Terminal Amine: hydrophilic, active form binds to Na+ receptor on the nerve membrane, inside the cell.



Local Anesthetic: Properties

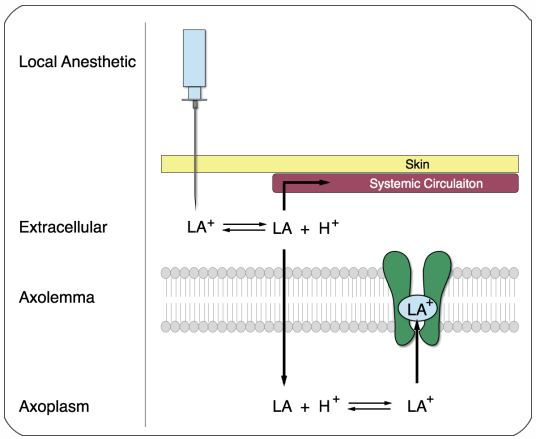
- Weak base: poorly water soluble, hydrochloride salts
- Packaged in an acidic solution: pH 4 – 7
- Most exist in ionic, quaternary state (+)

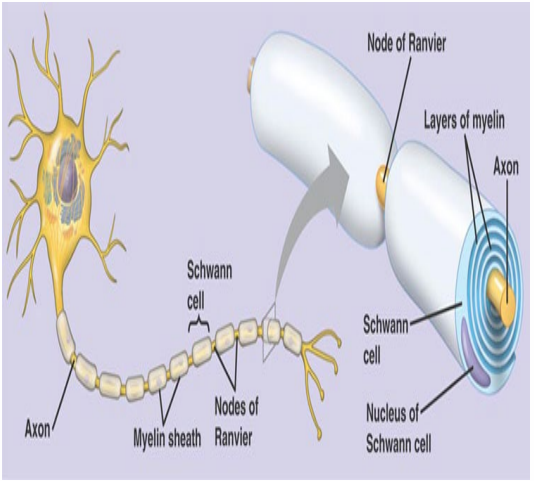


Mechanism of Action

1st: Unionized (lipid-soluble) base crosses the lipophilic nerve sheath to gain access to Na+ channels within the nerve membrane

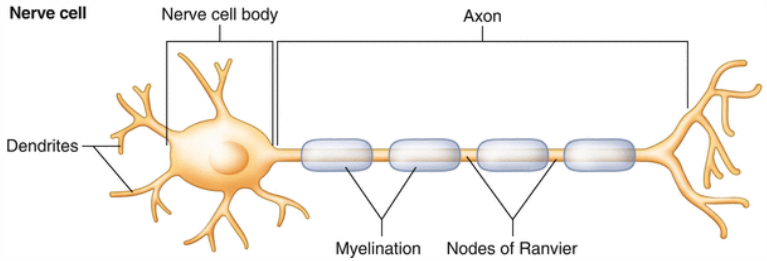
2nd: Once inside, LA become ionized binding more avidly to Na+ channels within cytoplasm, inhibiting depolarization.





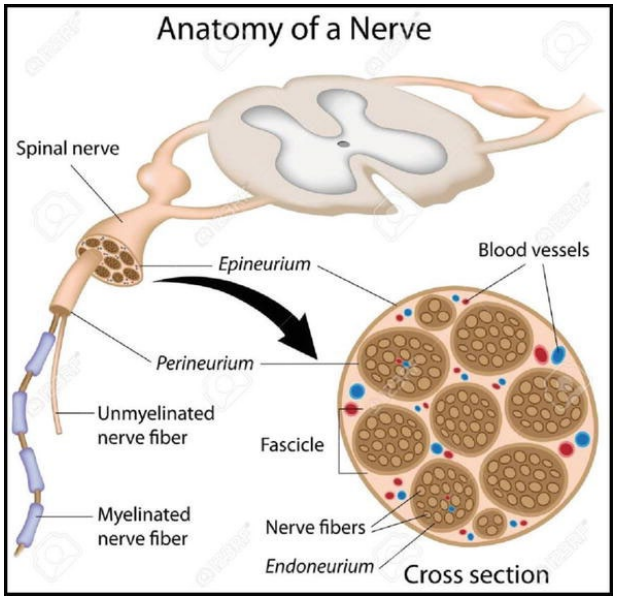
- Impulses travel very fast along myelin to nodes of Ranvier where Na+ channels in the axon are concentrated

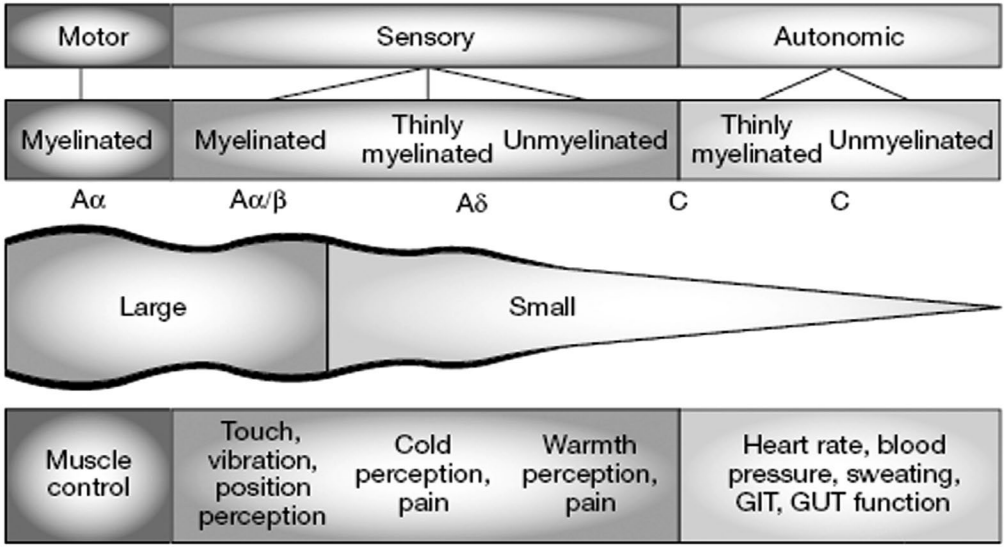
- Local Anesthetics must act on 2 -3 nodes to block impulse transmission



Local Anesthetic: Differential Blockade

- Deposited close to nerve sheath, USGRA
- Diffusion from outer surface to inner core along a concentration gradient.
- Factors affecting nerve conduction block
  - Tissue pH
  - Drug Concentration
  - Nerve morphology (type, size, myelination, location)
  - Drug properties (pKa, lipid solubility, protein binding)
  - Additives (NaHCO3, Epi)





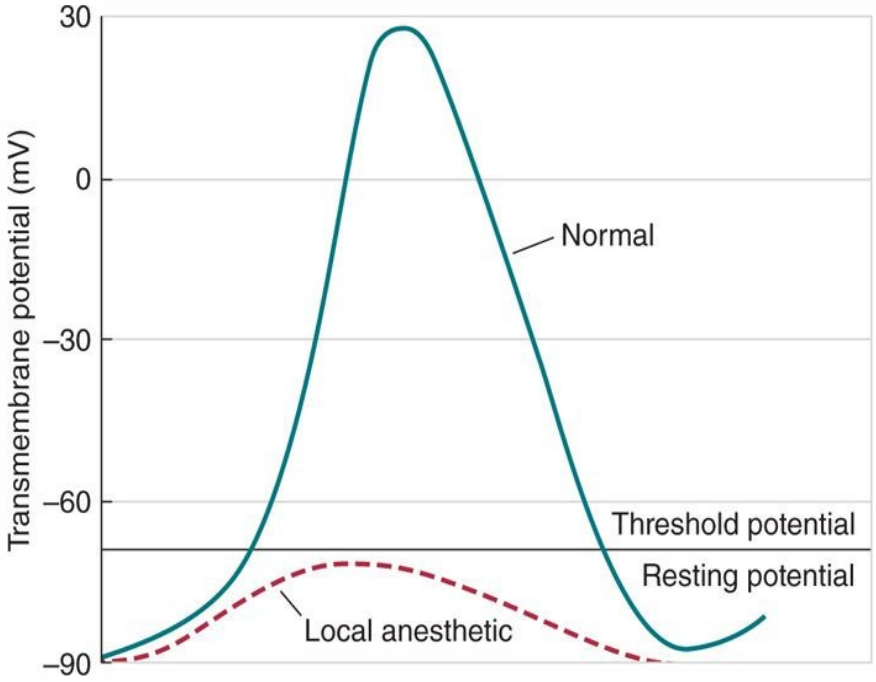
Local Anesthetic Effect on Nerve Conduction

1. Threshold for electrical excitability gradually increases

2. The rate of rise of the action potential declines

3. Impulse conduction slows

4. Bind more readily to Na+ channels in “open” “inactivated” state

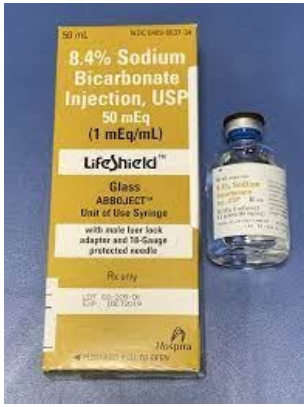


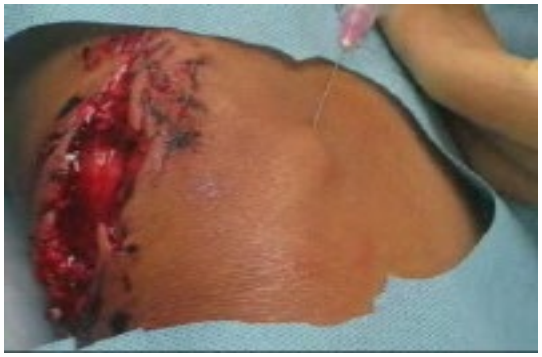
pKa → Onset of Action

- pKa influences **Speed of Onset of Action**
- pKa of most local anesthetics: 7.4 – 9.0

Agent	pKa	% Un-ionized at pH 7.4	Relative onset of Action
Procaine	8.9	Slow	Slow
Tetracaine	8.6	14	Slow
Bupivicaine	8.1	17	Moderate
Ropivicaine	8.1	----	----
Chloroprocaine*	9.1	2	Fast*
Lidocaine	7.7	24	Fast
Etidocaine	7.7	33	Fast
Mepivicaine	7.6	39	Fast

- Wound infection (acidosis) increases the ionized drug fraction ❾less drug available to permeate across lipid membranes and bind to intracellular Na+ receptor





- Increasing tissue pH - add NaHCO3 to LA solution (1ml to 9ml of LA)
  - speeds onset time and
  - increases the % of the lipid soluble LA

Potency & Duration of Action

- **Lipid solubility** determines anesthetic potency
  - Highly lipophilic, lipid soluble easily permeate nerve cell membranes, enter intracellularly = greater degree of blockade (AKA “dense” block)
  - Can contribute to a greater risk of toxicity

- **Duration of action**
  - Higher lipid solubility → higher protein binding = < free LA in systemic circulation
  - Small volume, higher concentration = longer and denser
  - High volume, low concentration = shorter and less dense
  - DoA varies by Proximity to nerve, use of vasoconstrictors, vascularity of tissue

ANESTHETIC	ONSET (min)	DURATION OF ANESTHESIA (h)	DURATION OF ANALGESIA (h)
3% 2-Chloroprocaine (+HCO_3)	10–15	1	2
3% 2-Chloroprocaine (HCO_3 + epinephrine)	10–15	1.5–2	2–3
1.5% Mepivacaine (+ HCO_3)	10–20	2–3	3–5
1.5% Mepivacaine (+ HCO_3 plus epinephrine)	10–20	2–5	3–8
2% Lidocaine (HCO_3 + epinephrine)	10–20	2–5	3–8
0.5% Ropivacaine	15–30	4–8	5–12
0.75% Ropivacaine	10–15	5–10	6–24
0.5% Bupivacaine or levobupivacaine (+ epinephrine)	15–30	5–15	6–30

Pharmacokinetics:

Absorption: influenced by

- Site of injection
- Dose & Type of LA
- +/ - vasoconstrictor
- Absorption → systemic circulation removing LA from its site of action = termination of its effect

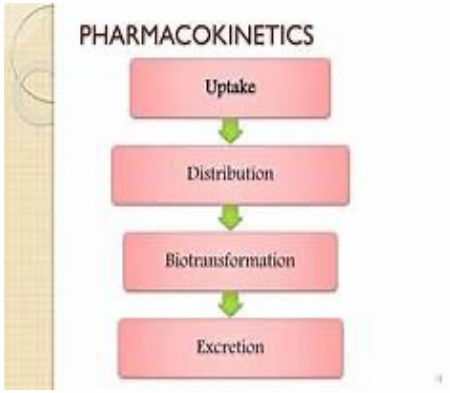
Distribution:

- 1st to highly perfused tissues,
- then redistributed to less
- perfused tissue
- Amides > Esters

Pharmacokinetics:

Uptake/ Metabolism:

- Based on chemical classification.
  - amino esters are hydrolyzed in plasma by the enzyme cholinesterase
  - amino amides are primarily metabolized in the liver by microsomal enzymes
- Higher levels of vascular uptake → higher plasma concentration → toxicity



Excretion/ Elimination:

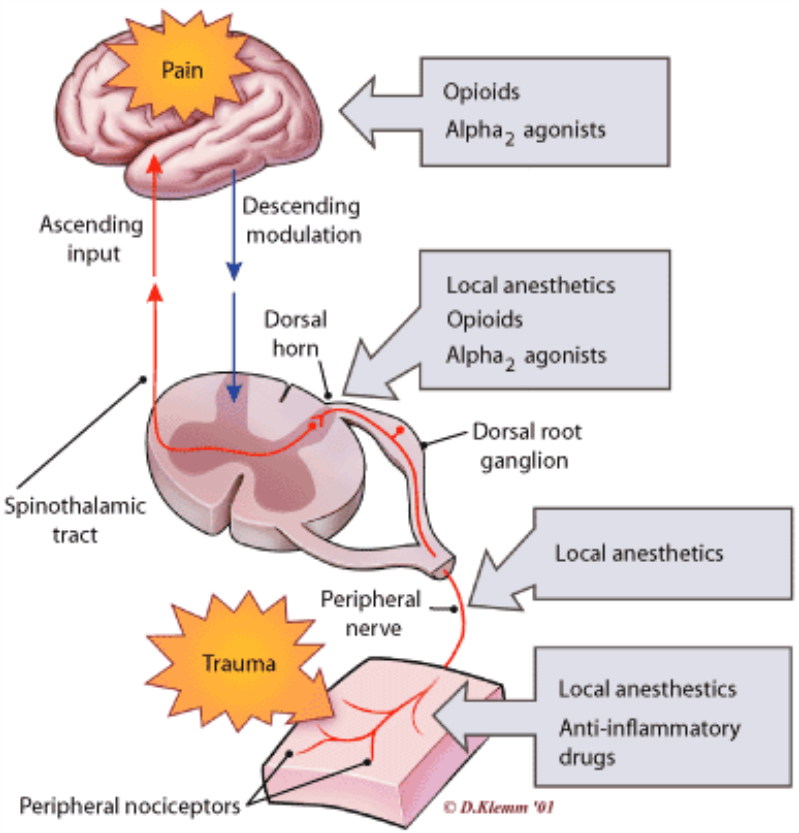
- LA & metabolites excreted by the kidneys.
- Less than 5% excreted in an unchanged form.
- Factors delaying elimination:
  - age (neonates & geriatric patients)
  - Clinical status of the patient (e.g. liver disease)

Physiological Response to Surgical Pain

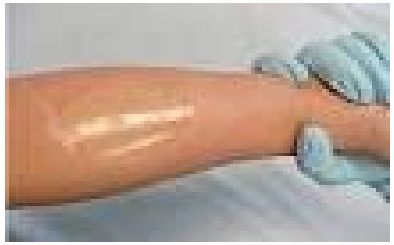
Reaction to noxious stimuli (e.g. surgical trauma):

1. Locally ❾inflammatory reaction: important for healing and defense against infection.

2. General ❾endocrine metabolic activation, hypermetabolic state.



Topical Block

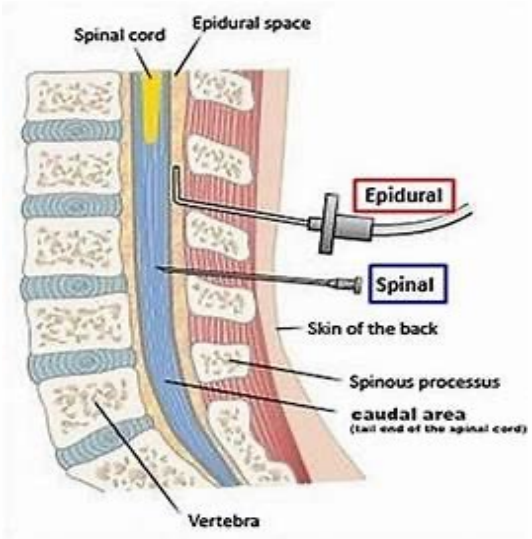


Local Infiltration

Central Neuraxial Block

Epidural Anesthesia

- Local anesthesia deposited at any point of the spinal column
- Provides a finite band of sensory blockade (possible motor)

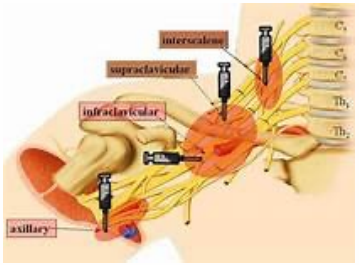


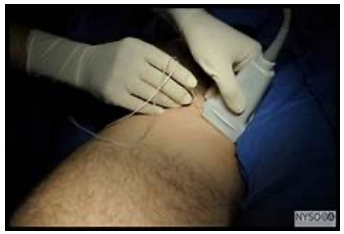
Spinal Anesthesia (Subarachnoid Block)

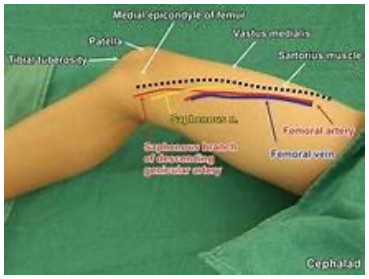
- Local anesthesia deposited in CSF to produce a block below the level of T10
- (T4 – C-section)
- Provides complete anesthesia for surgery

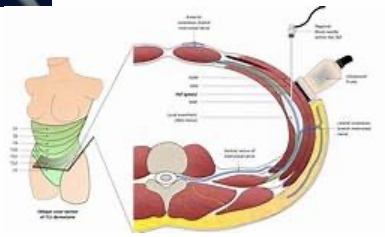
Peripheral Nerve Block

- Local anesthetic injected around nerve beds involving the operative site via USG









Examples: Brachial plexus, Femoral, Sciatic, TAP, Fascia Iliaca, Abductor Canal, Quadratus Lumborum, Pectoralis etc… Blocks

Peripheral Nerve Catheters

- Patients can receive single shot injection (surgical) in preop followed by catheter to be used postoperatively (pain control)
- Encourages early ambulation and minimizes narcotic use to utilize a multimodal anesthesia regimen
- Ropivacaine 0.2%

- May still require a multimodal regimen but will take the edge off
  - Methocarbamol, Gabapentin, Tylenol, Ketorolac, short acting opioids
- Can be maintained for 7 days
  - Exceptions include infection sites, migration of catheter, obstruction, disconnection

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ORIGINAL RESEARCH

Regional Anesthesia for Pain Management After Orthopedic Procedures for Treatment of Lower Extremity Length Discrepancy

- Methods: Retrospective review of peripheral nerve catheter (PNC) protocol for postoperative pain management in patients undergoing elective limb-lengthening procedures.
- Measure total opioid consumption following 48 hrs in the postoperative period between groups.
- Results: N =70, 41 received general + regional anesthesia (RA); 29 were general anesthesia alone. In first 48 postoperative hours general + RA group had 1/3rd opioid use compared to the GA alone group.

J Laparoendosc Adv Surg Tech A. 2017 Sep;27(9):898-902. doi: 10.1089/lap.2017.0339. Epub 2017 Jul 25.

Use of Regional Anesthesia Techniques: Analysis of Institutional Enhanced Recovery After Surgery Protocols for Colorectal Surgery

Erik M Helander [1], Michael P Webb [2], Meghan Bias [3], Edward E Whang [4], Alan D Kaye [1], Richard D Urman [5]

Method: ERAS protocols for open and laparoscopic colorectal surgery from 15 different healthcare facilities mostly in North American and one in New Zealand.

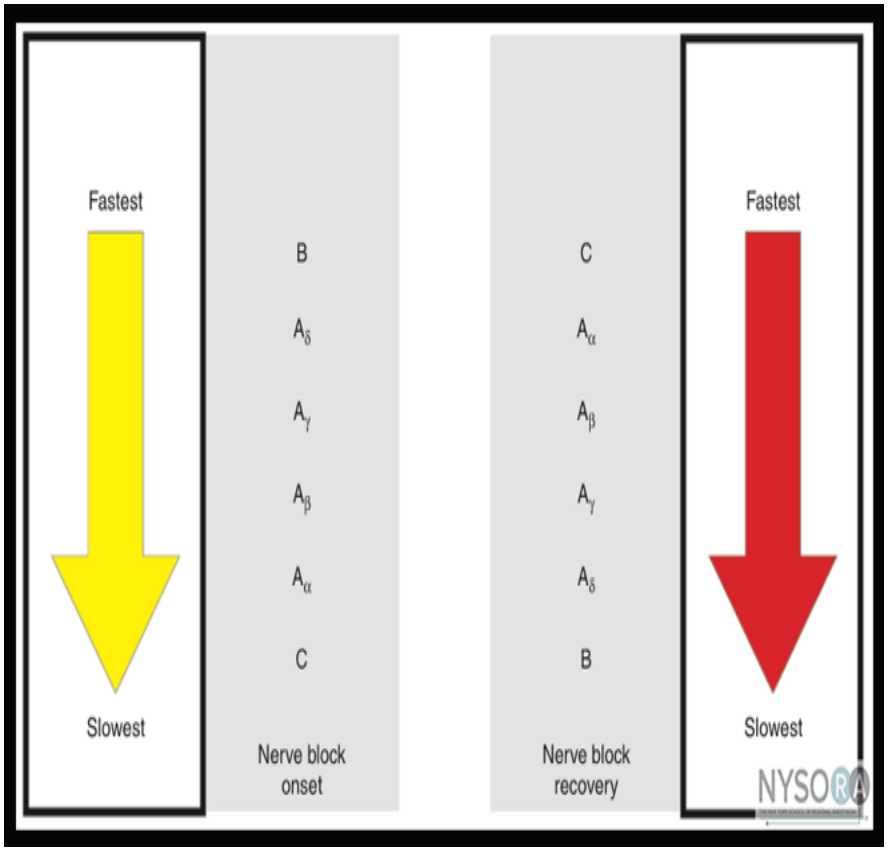
- Compared regional anesthesia recommendations.

Results: Most common regional technique was TEA. TAP blocks were the next most common.
Conclusion: Most protocols advocate for TEA use, 2/2 to lower incidence of paralytic ileus, attenuation of the surgical stress response, improved intestinal blood flow, improved analgesia, and reduction of opioid use.

Order of Sensory Function Block

Clinical Presentation

1. Pain sensation
2. Cold sensation loss
3. Warmth
4. Touch
5. Deep pressure
6. Motor function loss



Classification of Local Anesthesia

AMIDES (2 ’i’s)

- Lidocaine
- Mepivacaine
- Prilocaine
- Bupivacaine
- Ropivacaine
- Etidocaine

ESTERS

- Procaine (Novocain)
- Chloroprocaine
- Cocaine
- Tetracaine
- Benzocaine

Common LA for Regional Anesthesia

ANESTHETIC	ONSET (min)	DURATION OF ANESTHESIA (h)	DURATION OF ANALGESIA (h)
3% 2-Chloroprocaine (+HCO_3)	10–15	1	2
3% 2-Chloroprocaine (HCO_3 + epinephrine)	10–15	1.5–2	2–3
1.5% Mepivacaine (+ HCO_3)	10–20	2–3	3–5
1.5% Mepivacaine (+ HCO_3 plus epinephrine)	10–20	2–5	3–8
2% Lidocaine (HCO_3 + epinephrine)	10–20	2–5	3–8
0.5% Ropivacaine	15–30	4–8	5–12
0.75% Ropivacaine	10–15	5–10	6–24
0.5% Bupivacaine or levobupivacaine (+ epinephrine)	15–30	5–15	6–30

LA Class: ESTERS

- Metabolized by pseudocholinesterase to PABA
- PABA → S.E. = allergic reaction
- Short half life, relatively non-toxic
- Cocaine - metabolism in the liver, some in plasma

LA Class: AMIDES

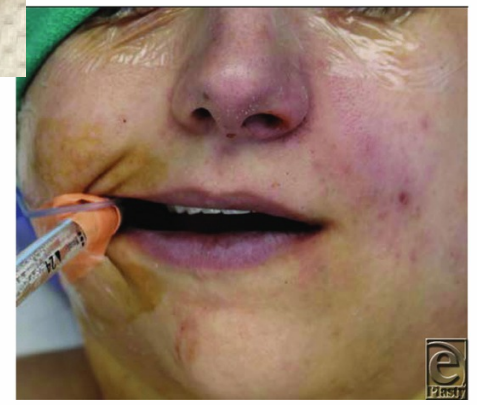
- Metabolized by the liver microsomal enzymes
- Longer half life, more toxic
- True allergy is VERY rare
- Bupivacaine: Racemic mixture → Toxicity > CV depression Narrow therapeutic index.
  - Highly lipid soluble → targets largely myelinated **motor** neurons
- Ropivacaine: Levo-isomer. Less lipophilic, **less potent,** less cardiotoxic. Duration varies 8-24 hrs of analgesia.
  - 20-30% less equipotent to Bupivicaine

AMIDE Dosing Guidelines

Amide-Type	Max Dose (mg/kg)	Max Total Dose (mg)
Levobupivacaine	2	150 mg
Bupivacaine	2.5	175 mg
Bupivacaine with epinephrine	3	200 mg
Lidocaine	4.5	300 mg
Ropivacaine	3	200 mg
Mepivacaine	7	400 mg
Lidocaine with epinephrine	7	500 mg
Prilocaine	8	If < 70 kg → 500 mg If > 70 kg → 600 mg

Prilocaine

- Intermediate-duration amino amide
- Lidocaine 2.5% + Prilocaine 2.5%
- No vasodilatation →increased volume of distribution = reduced CNS toxicity (unlike lido)
- dose-dependent methemoglobinemia (metabolism of the aromatic ring to o-toluidine). Rx: Methylene Blue 1-2mg/kg
- > 8 mcg/ml total dose administered (doses > 500 mg)
  - ➢ Peak MetHgB levels occur in 4-8 hrs



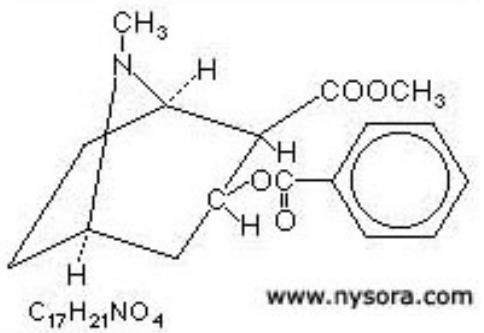
Exparel (liposomal bupivacaine suspension)

- FDA approved: October 2011for surgical site infiltration
- Produces reliable plasma levels of bupivacaine ~72 hours following infiltration
- Dilute in sterile saline. Dilution with Bupivacaine or Lidocaine can disrupt the carrier, and accelerate release of bound bupivacaine resulting in toxicity
- Additional local anesthetic is not recommend 96 hours following liposomal bupivacaine administration.
- Do not administer exparel within 72 hrs following initial administration
- Phase 3 trial showed patients receiving exparel had **less pain** and fewer patients required lipid rescue compared to placebo

ESTER Dosing Guidelines

Ester-Type	Max Dose (mg/kg)	Max Total Dose (mg)
Procaine	7	350 – 600
Chloroprocaine	11	800
Chloroprocaine with epinephrine	14	1000

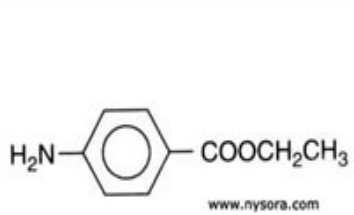
COCAINE



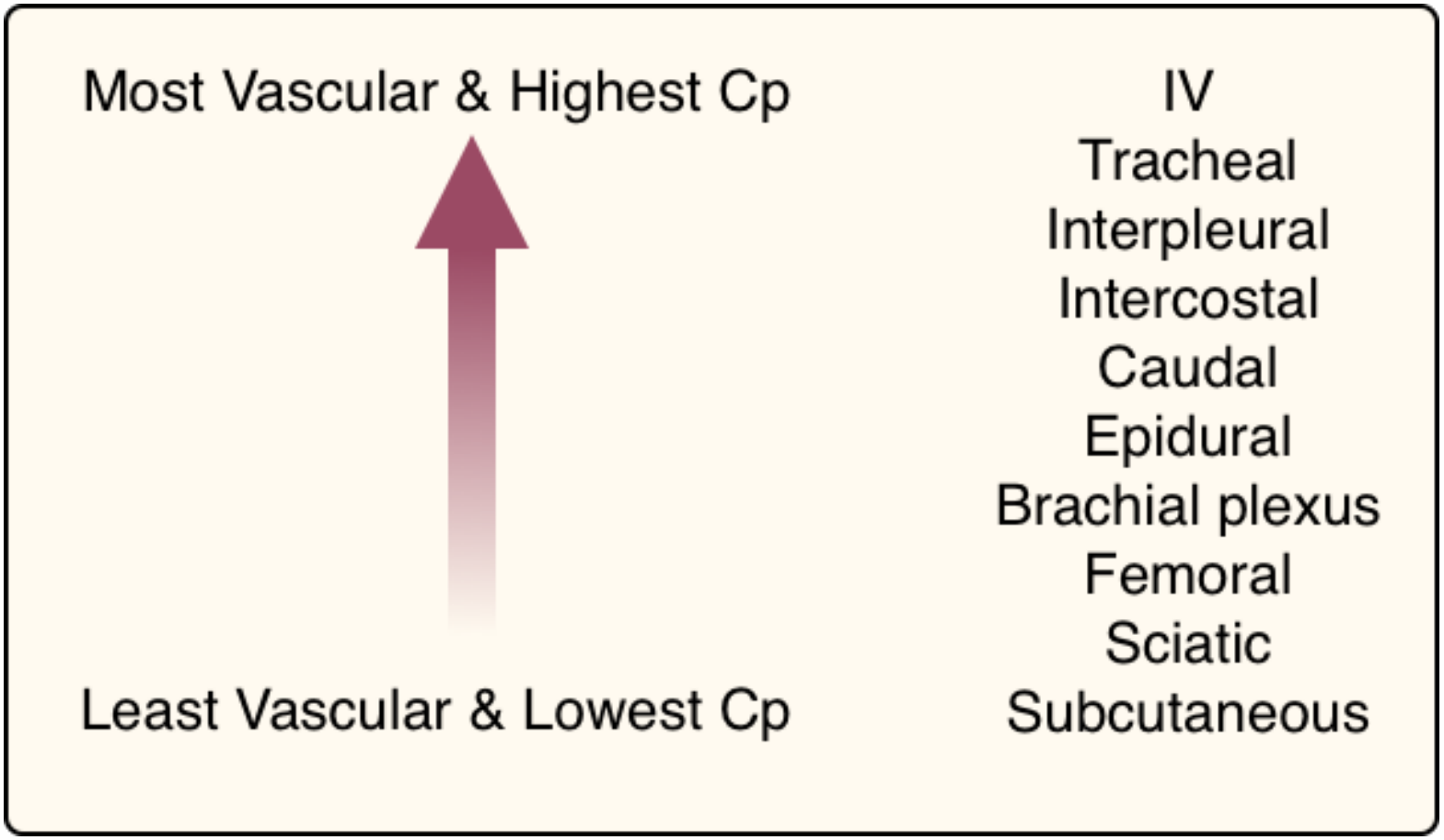
- Topical use only (e.g. nasal mucosa)
- Safe dose = 3 mg/kg (150 – 200 mg)
- Sensitizes myocardium to catecholamine
- DoA 30 min, maximum effect w/in 5 min
- Metabolized by the liver

BENZOCAINE: HURRICANE SPRAY

- Almost water insoluble
- Onset ~ 1 min.
- DoA: 15 - 20 min.
- Limited to topical application - oral
- (Hurricane spray = 20% Benzocaine)
- Side effect = Methemoglobinemia
- Pka of 3.5 (100% unionized)



Site of Injection & Tissue Blood Flow



Vasoconstrictors

- Epi delays vascular absorption, increasing duration
- Block prolonged ~ 50% and less systemically
- Effect > with Lido
- Effect < with Ropi
- Can warn of accidental IV injection of LA

Concentration Lidocaine HCl	Epinephrine	Lidocaine HCl (anhyd.) mg/mL	Epinephrine mcg/mL	Sodium Chloride mg/mL
0.5%	1:200,000	5	5	8
1%	1:200,000	10	5	7
1.5%	1:200,000	15	5	6.5
2%	1:200,000	20	5	6
1%	1:100,000	10	10	7
2%	1:100,000	20	10	6

Side Effects & Allergy

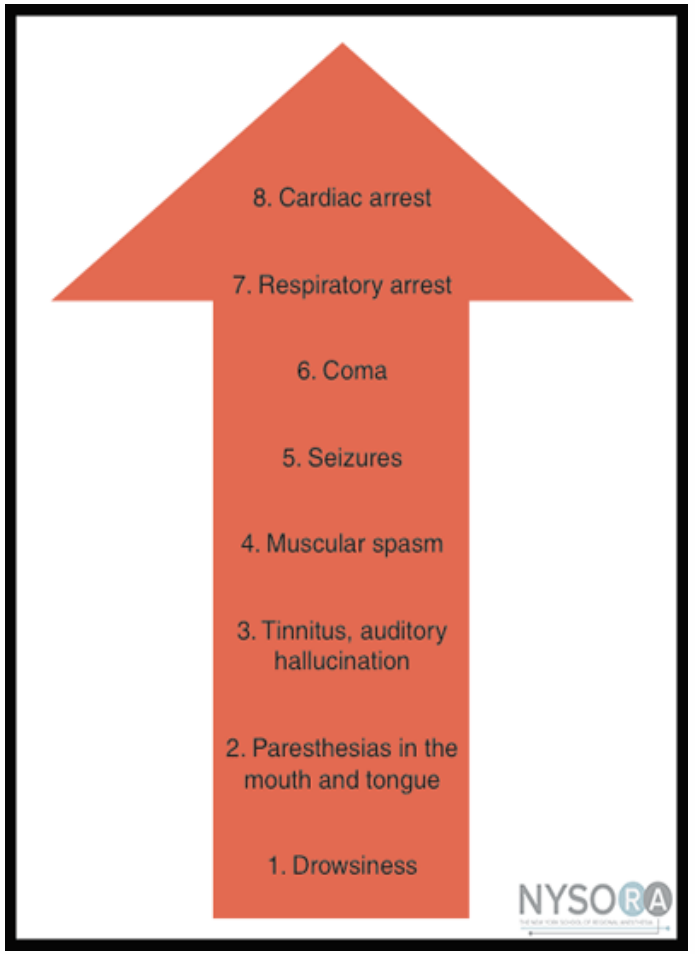
- Tinnitus, Circumoral numbness, Metallic taste
- Allergic reactions are rare < 1%

- Esters Types yield PABA, contributes to allergy
- Methylparaben preservative exist in both types of LA

- **ALWAYS** use preservative free solutions for SAB and Epidurals

Local Anesthetic Systemic Toxicity (LAST)

- Large amount of LA reaches systemic circulation
- Cardiac toxicity is electrophysiologic + contractile dysfunction
- Bupivacaine (lipophilic and high affinity for voltage gated sodium channels) →cardiotoxic
- Within 1 minute of LA injection but can present later (>1 hr)
- Variables: LA and dose, site of injections, comorbidities (organ dysfunction), extremes of age, small size or limited muscle mass
- More lipophilic (bupi) > less lipophilic (mepivacaine, lidocaine)



Treatment for L.A.S.T

- Focus on ensuring adequate ABC's
- Monitor for and treat Seizures: Benzodiazepines
- Ensure the availability of emergency equipment prior to block placement
- Avoid hypoxia and hypercarbia
- Ensure adequate ventilation & oxygenation
- Intralipid Therapy

Intralipid Therapy: MOA

- Reverse LA cardiotoxicity by increasing clearance from cardiac tissues
- Nonspecific extraction of LA from aqueous plasma or cardiac tissue, AKA (“lipid sink”)
- Counteracts LA inhibition of myocardial fatty acid oxidation, enabling energy production & reversing CV depression

Rx for LA Toxicity: Intralipid Therapy

www.lipidrescue.com

Rx for LA induced cardiac arrest

- Intralipid 20% Fat Emulsion
- 1.5 ml/kg over 1 min.
- Infusion 0.25 ml/kg/min
- CPR
- Repeat bolus Q 3-5 min (up to 3 ml/kg)
- MAX total dose 8ml/kg

Helpful Websites

- NYSORA.com
  New York School of Regional Anesthesia
- ASRA.com
  American Society of Regional Anesthesia
- www.lipidrescue.com

The End:

Thank you for the opportunity