Local Anesthetics: Present and Future

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Society for Pediatric Anesthesia
Spring Meeting 2013
Disclosure

• Drs. Berde, Kohane, Langer, and Strichartz share patents on several approaches to prolonged duration local anesthesia.
Disclosure

• We have received past research funding from Purdue Pharma and WEX Pharmaceuticals and currently have a collaboration agreement with Proteus SA for development of prolonged-duration local anesthetics.
Disclosure

• In the event of future commercial development, these investigators, our departments, Children’s Hospital and Brigham and Women’s Hospital could all receive royalties
The pronoun “we” in this lecture includes:

- Dan Kohane
- Gary Strichartz
- Jean-Xavier Mazoit
- Joanne Curley
- Jennie Castillo
- Robert Wilder
- Navil Sethna
- Min Xiao
- Mary Ellen McCann
- Gabriel Corfas
- Ru-Rong Ji
- Clifford Woolf
- Robert Langer
- Delphine and Rosa Hu
- Jeong-Ok Lim
- David Masters
- Brian Cairns
- Giulio Gambarota
- Christiane Draeger
- Chen Wang
- Helene Beloiel
- Barak Yahalom
- Matt Wylie
- Alberto Rodriguez-Navarro
- David Zurakowski
A Better Local Anesthetic: The Holy Grail of Regional Anesthesia
Aims of the Lecture - 1

1. To review of limitations of current-day local anesthetics
2. To describe some recent research on improved delivery of local anesthetics
3. To summarize research on the subtypes of sodium channels and their roles in diseases with pain insensitivity or spontaneous pain.
Aims of the Lecture - 2

4. To summarize recent efforts targeting sodium channel subtypes for analgesia and local anesthesia

5. To outline an approach to prolonged duration local anesthesia and sensory selective local anesthesia.
Currently Available Local Anesthetics are not Ideal.
Duration is too short.

- Bupivacaine and ropivacaine average durations: 10 hours with peripheral blocks
- Pain lasts for several days after major surgery.
Wound Infiltration During Surgery
Intercostal Blocks for Chest Surgery
Available Local Anesthetics Lack Sensory (or Nociceptive) Selectivity

- Motor block and autonomic block are usually, but not always undesirable.
- A truly pain-specific local anesthetic would be a great advance.
- Example: labor epidural without weakness or hypotension
Peripheral Nerve Blocks
for Orthopedic and General Surgery:
Ultrasound-Guidance has Transformed Practice
Systemic Toxicity of Local Anesthetics

- CNS -> seizures
- Cardiac -> arrhythmia, cardiac arrest
- Exacerbated by hypoxemia and acidosis.
- Resuscitation is difficult.
Local Tissue Toxicities of Local Anesthetics

- Nerve deficits
  - transient or permanent
- Muscle - necrosis
All Existing Amino-Amide and Amino-Ester Local Anesthetics are Inherently Neurotoxic and Myotoxic at the Concentrations in Clinical Vials.

(Strichartz et al)
• We don’t grossly injure nerves every day only because delivery into nerves is usually inefficient.
• Prolonged perineural delivery increases the risk for nerve injury.
• Other risk factors: ischemia, restricted compartments, hypotension, pre-existing neuropathy, ....
What new local anesthetics have been developed in the past 40 years?
Chiral local anesthetics

• Ropivacaine
• Levo-bupivacaine
• \( \leq 2 \)-fold improvements in therapeutic index
• very slight improvement in sensory selectivity for ropivacaine
• No important prolongation of analgesia
Why haven’t the pharmaceutical companies developed new local anesthetics?

- Market is reasonably large
  (> $1 billion/year)
- Developing new drugs costs money
  (> $200 million through Phase 3)
Business Models Favor Oral Drugs Taken Every Day for Chronic Illnesses

• The average American has 4 – 6 surgeries per lifetime.

• Example: Astra (now Astra-Zeneca) makes acid blockers and drugs for asthma/COPD.

• Example: > 20 different controlled-release oral opioids
Approaches to Prolonged Duration

- Additives (vasoconstrictors, ketamine)
- Controlled release of existing local anesthetics
- New drugs
- “Controlled” neurolysis
Alternatives for Neurodestructive Blockade

- Neurolytics
- Butamben
- Radiofrequency Lesioning
- Cryotherapy
Additives

• Adrenergics
  (epinephrine, phenylephrine, clonidine)
• Ketamine
• Unlikely to get more than 18 hours.
Controlled-Release of Bupivacaine and Other Local Anesthetics

- Liposomes
- Depo-Foam
- Polymer Microparticles
Problems with Controlled-Release

• Narrow therapeutic window: burst release could be fatal
• Local anesthetics are very low potency drugs.
• Stability of the vehicle
• Storage and reconstitution
Examples:

• Leuprolidine (Lupron): releases about 83 micrograms/day from microspheres, over about 3 months.

• Bupivacaine in liposomes or microspheres: may require 20 mg/hour!
Microspheres containing Bupivacaine 70% with Dexamethasone 0.05% and PLGA Polymer 29.5%
Phospholipid-Based Delivery Systems
Bupivacaine in Liposomes

- Some have had inflammatory responses and neurotoxicity
- Unpredictable duration
- Problems with stability in real-world use
Bupivacaine in Lipid Depot Foam
Exparel

- Recent FDA approval
- To date, 4 published clinical trials
- All with wound infiltration, none with perineural injection
Exparel – Clinical Trials and Use

- Hemorrhoids, bunions, breast reduction, knee surgery
- PK shows safe blood concentrations with bupivacaine doses from 150 – 600 mg
- Higher doses showed some reductions in pain scores or opioid use compared to controls.
Pain Scores with Movement After Wound Infiltration for Knee Arthroplasty

Figure 4. Pain Intensity With Activity

*P<0.05 versus Bup/lepi 150 mg.
Abbreviations: Bup/lepi = bupivacaine HCl with epinephrine; DB = Diprospan bupivacaine.
Amitriptyline as a Prolonged Duration Local Anesthetic

- Peter Gerner and coworkers
- Tricyclics are also sodium channel blockers.
- Lipophilic
- Neurotoxicity and possible ways to minimize it.
- Clinical status remains uncertain.
Site 1 Sodium Channel Blockers Derived from Marine Toxins

- Structure of NeoSTX,
- Puffer fish
- Red-tide “bloom” on a seacoast
Site 1 sodium channel blockers

- e.g. tetrodotoxin, saxitoxin
- Very high potency on isolated nerve
- Minimal local neurotoxicity
- Minimal effect on cardiac muscle
- Minimal CNS entry
Site 1 sodium channel blockers

- Extremely hydrophilic
- Much lower potency \textit{in vivo}
- Rapid systemic uptake produces diaphragm paralysis and hypotension.
Saxitoxins

![Saxitoxin structure](image)

<table>
<thead>
<tr>
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<th>R2</th>
<th>R3</th>
<th>R4</th>
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<td>-H</td>
<td>-H</td>
<td>-H</td>
<td>-CONH₂</td>
</tr>
<tr>
<td>Neosaxitoxin</td>
<td>-OH</td>
<td>-H</td>
<td>-H</td>
<td>-CONH₂</td>
</tr>
<tr>
<td>Decarbamoyl Saxitoxin</td>
<td>-H</td>
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Tetrodotoxin

![Tetrodotoxin structure](image)
Local Anesthetics

> 97% of dose

Injection or absorption site → Central Circulation

< 3% of dose

↓ ↑

Effect Site → Metabolism and elimination
Combinations of site-1 toxins with bupivacaine show synergistic prolongation of sensory blockade
Epinephrine dramatically increases the potency of site 1 toxins in nerve blockade.
Epinephrine prolongs nerve blockade by > 10-fold.
Studies on TTX, STX, NeoSTX 1998 - 2008

- Kohane, Strichartz, Berde et al
- Rat sciatic nerve blockade in vivo
- Safety and efficacy studies
- Adrenergic receptor pharmacology
- Saxitoxin series: STX, NeoSTX, dcSTX
Studies on TTX, STX, NeoSTX 1998 - 2006

• Prolonged blockade in models of inflammation or nerve injury
• Differential effects of TTX versus Bupivacaine on local, systemic and spinal activation of cytokines, MAP kinases, …
• Helene Beloeil, Ru-Rong Ji et al
• Papers in Anesthesiology
Lost in Translation (2002-2008)

• Previous licensure and development of bupivacaine microspheres with Purdue Pharma
• Reluctance of many large pharma companies to invest in a new local anesthetic
• Ropivacaine and levo-bupivacaine lost lots of money.
• Omigod! It’s a toxin!!!!
Other Local Anesthetic Research While Waiting to Develop New Drugs (2002-2008)

- Models for Tachyphylaxis and Inflammation-Induced Local Anesthetic Failure
- Ontogeny of Local Anesthetic Actions in Developing Animals
- Effects of Prolonged Blockade with Local Anesthetics and Site 1 Toxins on Models of Inflammation and Nerve Injury
Partner #1 - WEX Pharmaceuticals

- Canadian-Chinese company, previously public, now private
- Production process for TTX from puffer fish via aquaculture in China
- Focus on TTX for systemic analgesia for refractory cancer pain and neuropathic pain.
Partner #2 - Proteus SA

Why Development in Chile?

• Chile has a huge seafood industry, and a huge problem with red tide and paralytic shellfish poisoning.

• University of Chile Santiago: world-class chemists and toxicologists on site 1 toxins
Partner #2 - Proteus SA

- A unique strain of cyanobacterium found in Santiago Chile produces neosaxitoxin (NeoSTX) in enormous yield.
- A production process generates NeoSTX at very high purity.
• Alberto Rodriguez-Navarro: a unique general surgeon who focused on postoperative pain.

• Became interested in local anesthesia, read Henrik Kehlet’s papers, read our work on site 1 toxins, was aware of the work on site 1 toxins at the University of Chile Santiago.

• He asked the question “why hasn’t this gone from rats to humans?”

• Developed pure formulation of NeoSTX for injection.
• Initial development program through the Chilean ISP (local regulatory authority, corresponds to FDA in some respects)
• No drug had ever been developed from bench to IND before the Chilean ISP before.
• 2006-2007 Pre-clinical program (academic, non-GLP)
• 2007 Phase I Trials
• 2007-8 Proteus SA – small biotech company
• 2008-9 Phase 2 Trials conducted
• 2009-2010 Negotiations and Partnership between Proteus and CHB
Clinical Trials in Chile

- Phase 1 - skin infiltration in volunteers
  - NeoSTX: more prolonged skin numbness compared to bupivacaine.
  - NeoSTX + bupivacaine: more prolonged numbness than NeoSTX alone or bupivacaine alone
  - NeoSTX was well tolerated- no local or systemic toxicities.

Phase 2  RCT Superiority Trial

- 137 patients undergoing laparoscopic cholecystectomy, general anesthesia
- Double blind comparison to bupivacaine
- Infiltration of incisions
- Primary outcomes: pain scores at 12 and 24 hours
- Secondary outcomes: global recovery scale, safety

Rodriguez-Navarro et al
Regional Anesthesia and Pain Medicine
2011; 36:103-109
Pain Relief:
When comparing Bupivacaine and NeoSTX patients, NeoSTX patients:
- Were less likely to experience severe pain
- Were more likely to experience complete pain relief

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- Were less likely to experience severe pain
- Were more likely to experience complete pain relief
Results

When comparing Bupivacaine and NeoSTX patients, NeoSTX patients:
- recovered almost 2 days sooner (3.8 days vs. 5.7 days).
NeoSTX: Phase 2 Laparoscopy Trial

• Postoperative Recovery
  – By a composite global measure of quality of postop recovery, patients felt fully recovered almost 2 days sooner (3.8 days vs. 5.7 days).

“Surrogate Vital Capacity”

- Control
- 1 μg/kg i.v.
- 1 μg/kg s.c.
- 2 μg/kg s.c.
- 2 μg/kg s.c. + Bupiv.
- 3 μg/kg s.c.
Hemodynamic Changes after NeoSTX

**Graphs:**
- **Resistance (Woods units):**
  - Y-axis: 0 to 100
  - X-axis: 0 to 180 minutes
  - Legend: CO, SVR, PVR
- **Cardiac Output (l/min):**
  - Y-axis: 0 to 3
- **Blood Pressure (mmHg):**
  - Y-axis: 0 to 160
  - X-axis: 0 to 180 minutes
  - Legend: HR, SBP, DBP, MAP
- **Heart Rate (bpm):**
  - Y-axis: 0 to 160
  - X-axis: 0 to 180 minutes

**Legend:**
- 1 μg/kg
- 2 μg/kg
- 3 μg/kg

* indicates statistical significance.
NeoSTX Current Status

- IND under FDA review
- Phase 1 volunteer dose-escalation study in Boston
- Dr. Joseph Cravero is the PI.
Approaches to Sensory-Selective or Nociceptive-Selective Local Anesthesia

• Targeting Drug Entry into Small Fibers
• Targeting Sodium Channel Subclasses
Targeting Local Anesthesia to C-Fibers and A-delta Fibers

**Primary Afferent Axons**

<table>
<thead>
<tr>
<th>Axon Type</th>
<th>Diameter (μm)</th>
<th>Speed (m/s)</th>
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<tbody>
<tr>
<td>$\alpha$</td>
<td>13-20</td>
<td>80-120</td>
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<tr>
<td>$\beta$</td>
<td>6-12</td>
<td>35-75</td>
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<tr>
<td>$\delta$</td>
<td>1-5</td>
<td>5-35</td>
</tr>
<tr>
<td>C</td>
<td>.2-1.5</td>
<td>.5-2.0</td>
</tr>
</tbody>
</table>
Sensory-Selective (Nociceptive-Selective) Nerve Blockade
Binshtok, Bean and Woolf  Nature 2007  449: 6-7-610

• TRPV1 channels are located in small sensory fibers, not large fibers.
• Capsaicin, the substance that makes chili peppers hot, opens TRPV1 ion channels in small sensory fibers.
• Open TRPV1 channels permit entry of the quaternized lidocaine analogue QX-314
Lidocaine facilitates QX-314 sensory-selective blocks in rats and mice.

Binshtok et al  Anesthesiology July 2009

• Lidocaine + QX-314 produced much longer blocks than QX-314 alone.

• Capsaicin appeared to produce pain on injection, lidocaine did not.
Surfactants facilitate QX-314 sensory-selective blocks in rats and mice.

Sagie and Kohane
Proceedings of National Academy of Sciences USA
Feb. 2010

• Surfactants appear to preferentially facilitate QX-314 entry into unmyelinated (C) or thinly myelinated (A-δ) fibers more than into thickly myelinated (A-β) fibers
9 Major Sodium Channel Subtypes
$\text{Na}_v\ 1.1$ – $\text{Na}_v\ 1.9$

- Differential expression in normal development
- Differential expression in different tissues
- Differential expression following tissue injury, inflammation, or nerve injury
- Alterations in disease states “channelopathies” – seizures, migraine, cardiac rhythm disturbances
Na\textsubscript{v} 1.7 and Na\textsubscript{v} 1.8 Sodium Channel Subtypes

- Subtypes that are expressed only in small sensory fibers, not in motor fibers, CNS, cardiac muscle, or skeletal muscle.
- Importance for elucidating diseases of increased pain and insensitivity to pain.
- Targets for more selective systemic analgesics.
- Targets for sensory-selective local anesthetics.
Na\textsubscript{v} 1.7 and Na\textsubscript{v} 1.8
Sodium Channel Subtype Blockers as Systemic Analgesics

• Screening of compounds
• Early preclinical studies of candidate molecules
µO-Conotoxin MrVIB

• Modified form of a paralytic toxin derived from cone snails
• Selective blocker of Nav1.8 sensory-specific sodium channels, found in small (Aδ and C fibers)
• Systemic administration in rats produced analgesia without motor weakness in models of neuropathic and inflammatory pain.
• Might be a useful systemic drug for neuropathic pain, probably not as a local anesthetic.
ProTX-II
Schmalhofer et al
Molecular Pharmacology 2008
(Merck)

• Derived from tarantula venom
• Selective blocker of Nav1.7 sodium channels in vitro
• Effective on de-sheathed C-fibers
• Ineffective in models of acute and inflammatory pain
A-803467    Nav 1.8 Blocker
Jarvis et al  PNAS 2008
Abbott Labs

• Effective in some rat neuropathic pain models
• Effective for Freund’s adjuvant inflammatory pain in rats.
• Ineffective for incisional pain, thermal pain, formalin-irritant pain in rats.
Conclusions

• Local anesthetics are useful.
• Currently-available local anesthetics have limitations.
• For improving success rates, visualize nerves and needles: location, location, location.
Conclusions

• Sodium channel subtypes may be important targets for better systemic analgesics, especially for neuropathic pain, and for better local anesthetics, with sensory-selectivity.

• Novel prolonged duration local anesthetics are under development.