Update on Prolonged Duration Local Anesthesia

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Disclosures (current)

Neosaxitoxin (NeoSTX): Dr. Berde and Dr. Kohane at Boston Children’s Hospital (BCH) have multiple issued patents on prolonged local anesthesia. Dr. Berde and BCH have an ongoing collaboration with Proteus SA, a Chilean biotech company, for development of NeoSTX. Dr. Berde has received no payments of any kind from Proteus.

In June 2015, BCH and Proteus signed a licensure and development agreement with Gruenenthal GmbH, a pharma company in Aachen, Germany.

In the event of future commercial development, Dr. Berde, his collaborators, Proteus, and BCH could potentially receive royalties and milestone payments.
Objectives of the Lecture

1. To appraise advantages and limitations of existing local anesthetics
2. To evaluate recent research on sodium channels and local anesthetic mechanisms and efforts towards developing new local anesthetics
3. To assess how new local anesthetics might change our clinical practice in the near future
The pronoun “we” in this lecture includes:

- Dan Kohane
- Gary Strichartz
- Jean-Xavier Mazoit
- Joanne Curley
- Jennie Castillo
- Robert Wilder
- Min Xiao
- Gabriel Corfas
- Ru-Rong Ji
- Clifford Woolf
- Roy Peake
- Paul Hickey
- The Entire TIDO Team, especially Rajinder Khunkhun and Irene Abrams

- Robert Langer
  - Jeong-Ok Lim
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  - Barak Yahalom
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- Joseph Cravero
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  - Carolina Donado
  - Kim Lobo
  - David Zurakowski
  - Joseph Kim
  - Takako Masuda
  - Scott Templin
  - Delphine Hu
  - Rosa Hu
Despite Major Advances, Surgery is Still Painful
Opioids are Partially Effective, but with Side-Effects and Risks

- Somnolence, Mental Clouding
- Respiratory Depression
- Nausea and GI Dysfunction
- Addiction
Prof. Henrik Kehlet’s “Laws” for Peri-Operative Care (> 800 Publications)

- Postoperative care as “acute rehabilitation”.
- Minimally-invasive surgery whenever possible.
- Multi-modal analgesia, regional anesthesia, NSAIDs, opioid-sparing
- Early removal of tubes, early feeding, mobilization and ambulation.
- Pain relief must be sufficient for movement, not just for lying still in bed.
Wound Infiltration During Surgery
Ultrasound has Transformed Regional Anesthesia
Ultrasound-Guidance Has Revolutionized Regional Anesthesia: Paravertebral Blockade for Infant Thoracotomy
Clinical Outcomes of Regional Anesthesia

• Improved Pain Scores
• Opioid Sparing
• Accelerated Recovery
  (Hospital Stay, GI Function)
• Long-Term Outcomes (Rehabilitation, Chronic Pain, Cancer Progression)
• Reduced Morbidity and Mortality
  (30 day, 6 month, 1 year)
Amino-Amide Local Anesthetics

Aromatic Group | Amide Bond | Tertiary Amine
Local anesthetics - Mechanism

Limit influx of sodium, thereby limiting propagation of the action potential.
Developing local anesthetic block

![Graph showing membrane potential over time](image)
Voltage-Gated Sodium Channels: Tertiary Structure
Extracellular

Intracellular

Voltage-gated Sodium Channel

\[ \bullet = \text{Na}^+ \]
Resting

Activated (Open)

Inactivated
Modulated Receptor Hypothesis

Resting

\[ \overset{\uparrow}{\text{Inactivated}} \]

\[ \overset{\rightarrow}{\text{Activated (Open)}} \]

= Local Anesthetic
Currently Available Local Anesthetics are not Ideal.
Local Anesthetics are “Dirty Drugs”.

- Low potency (10 – 300 mg)
- Toxicity near therapeutic dose
- Multiple cellular actions.
Other Sites of Action of Local Anesthetics

- Calcium channels
- Potassium channels
- TRPV1 receptor-channels
- Mitochondrial electron-transport
- Macromolecular assembly
Systemic Toxicity of Local Anesthetics

- CNS -> seizures
- Cardiac -> arrhythmia, cardiac arrest
- Exacerbated by hypoxemia and acidosis.
- Resuscitation is difficult.
Currently Available Local Anesthetics: Short Duration of Analgesia

- Bupivacaine and ropivacaine average durations: 10 hours with peripheral blocks
- Pain lasts for several days after major surgery.
- Catheter infusions are useful, but high-maintenance
Current-Day Local Anesthetics Pose Additional Problems in Pediatrics
Role of pH:

• Alters net charge on local anesthetics
• Influences solubility in aqueous and hydrophobic media.
• Influences transverse diffusion across biological membranes
Major Structural Constraint:

- Must dissolve well and diffuse rapidly in both aqueous and lipophilic micro-environments.
Most Drugs

Injection or absorption site → Central circulation → Effect site

Metabolism and elimination
Local Anesthetics

> 93% of dose

Injection or absorption site → Central Circulation

< 7% of dose

↓↑

Effect Site

↓

Metabolism and elimination
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
Nav\textsubscript{1.7} and Nav\textsubscript{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
Sodium Channelopathies in Painful Diseases

• Two clinically distinct diseases, involving different types of mutations the gene SCN9A, which encodes the Naᵥ 1.7 sodium channel
• Erythromelalgia
• Paroxysmal extreme pain disorder (PEPD) also known as familial burning rectal pain disorder – episodic burning pain in the rectum, eyes, and mouth.
Sodium Channel Subtype Blockers as Systemic Analgesics

- Screening of compounds
- Early preclinical studies of candidate molecules
Targeting Local Anesthesia to C-Fibers and A-delta Fibers
• 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 epub 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
Currently Available Local Anesthetics: Short Duration of Analgesia

- Bupivacaine and ropivacaine average durations: 10 hours with peripheral blocks
- Pain lasts for several days after major surgery.
- Catheter infusions are useful, but high-maintenance
FIGURE 3. Time to first pain, according to volume changes relative to 20 mL 0.375% (adjusted for concentration). Estimated median for 10, 20, and 40 mL = 10.0 (interquartile range, 9.5-11.5), 10.75 (interquartile range, 9.75-14.0), and 15.0 (interquartile range, 10.75-21) hours.
Randomized Study of the Effect of Local Anesthetic Volume and Concentration on the Duration of Peripheral Nerve Blockade.
Fredrickson, Michael; MD, FANZCA; Abeysekera, Amitha; White, Richard

FIGURE 4 . Time to first pain, according to concentration changes relative to 20 mL 0.375% (adjusted for volume). Estimated median for 0.375%, 0.5%, and 0.75% = 10.75 (interquartile range, 9.75-14.0), 11.5 (interquartile range, 10.0-16.75), and 13.75 (interquartile range, 10.5-21.0) hours.
Additives to Prolong Single-Shot Nerve Blocks

• Epinephrine
• Clonidine
• Dexamethasone
• Opioids (e.g. buprenorphine)
• Ketamine
• Many others.....
Dexamethasone (IV or Perineural) Prolongs Peripheral Nerve Blocks

Cummings K C et al.
Br. J. Anaesth. 2011;107:446-453
Clonidine Prolongs Peripheral Nerve Blocks

Fig. 3 Duration of postoperative analgesia. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of postoperative analgesia was defined as time until first analgesic request. Meta-analyses were performed using a fixed effect model, except *random effects model (P for heterogeneity). Symbols and horizontal lines are mean differences (single trials) or WMDs (combined data) with 95% CIs. CI = confidence interval; LA = local anesthetic, WMD = weighted mean difference.
Peripheral Nerve/Plexus Catheters Are Useful, but Labor-Intensive
Controlled-Release of Bupivacaine and Other Local Anesthetics

- Liposomes
- Depo-Foam
- Polymer Microparticles
Microspheres containing Bupivacaine 70% with Dexamethasone 0.05% and PLGA Polymer 29.5%
Bupivacaine-Dexamethasone Microspheres

• Licensed to Purdue Pharma
• Phase 1 and Phase 2 Trials in the early 2000s
• 2 – 3 days of strong analgesia
• Stalled in Phase 2
Phospholipid-Based Delivery Systems
Bupivacaine in Lipid Depot Foam (Exparel®)

- FDA approval for wound infiltration for postoperative analgesia
- Not sufficiently dense for surgical anesthesia
- Clinical trials mostly against placebo.
- > 24 hours of analgesia vs. placebo
- Small effect size from 24 – 72 hours
- Very rapid increase in sales in U.S.
- Not approved in Europe
Bupivacaine in Lipid Depot: Exparel® – Clinical Trials and Use

• Pivotal trials: hemorrhoids, bunions, breast reduction
• 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/spi = bupivacaine HC with epinephrine; DB = DepoBupivacaine.
Liposomal Bupivacaine in Peripheral Nerve Blockade
Cochrane Systematic Review

• Hamilton TW et al, 2016
• 7 studies completed, 3 not published
• Block locations: TAP, penile, ankle
• RCTs vs. placebo, aqueous bupivacaine, or no block
• **AUTHORS' CONCLUSIONS:** “A lack of evidence has prevented an assessment of the efficacy of liposomal bupivacaine administered as a peripheral nerve block. At present there is a lack of data to support or refute the use of liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain.”
Liposomal Bupivacaine Femoral Block for Total Knee Arthroplasty

- Hadzic et al. Anesthesiology 2016 124:1372-81
- RCT: liposomal bupiv. vs. placebo (saline) block
- Femoral catheter placed but not dosed initially
- 3-step rescue paradigm: i. episodic opioid, ii. PCA opioid, iii. femoral nerve catheter infusion
- 92% of liposomal bupivacaine group required PCA vs. 81% of placebo group
- Very modest impact on pain scores, mostly in first 24 hours
- No measurements of pain with movement or functional/rehabilitative outcomes.
Site 1 Sodium Channel Blockers
Derived from Marine Toxins

- Structure of NeoSTX,
- Puffer fish
- Red-tide 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
Rat Sciatic Nerve Block for Local Anesthetic Testing
Combinations of site-1 blockers with bupivacaine show synergistic prolongation of sensory blockade

(Kohane et al Anesthesiology 1998)
Epinephrine dramatically increases the potency of site 1 toxins in nerve blockade.

Note: Epi reduces ED50 for half-maximal sensory block by 4-fold
Epinephrine prolongs nerve blockade by > 10-fold.
Local Anesthetics

> 93% of dose

Injection or absorption site → Central Circulation

< 7% of dose

↓↑

Effect Site

↓

Metabolism and elimination
Regional Blood Flow in Muscle and Nerve

A

Peri-sciatic Muscle

TTX60μM

Blood Flow (ml · min⁻¹ · g⁻¹)

Time (min)

* †

B

Sciatic Nerve

Blood Flow (ml · min⁻¹ · g⁻¹)

Time (min)

C

TTX60μM with Epinephrine

D

Blood Flow (ml · min⁻¹ · g⁻¹)

Time (min)

Masuda, Cairns, Sadhasivam, Berde  Anesthesiology 2004
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
• Models of tachyphylaxis and inflammation-induced local anesthetic failure
• 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, Pain, ....
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!!!!
Neosaxitoxin (NeoSTX)
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

• A unique strain of cyanobacterium produces neosaxitoxin (NeoSTX) in enormous yield.
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
Compared to Bupivacaine patients, NeoSTX patients had lower pain scores, and were more likely to experience complete pain relief.

When comparing Bupivacaine and NeoSTX patients, NeoSTX patients, recovered almost 2 days sooner (3.8 days vs. 5.7 days).

Global Postoperative Recovery Score

![Graph showing the percent of patients attaining full recovery over days. The graph includes a line for Neosaxitoxin (n = 69) and a line for Bupivacaine (n = 68). Logrank test = 21.3, P < 0.001.]
NeoSTX FDA Process

• Pre-IND Meeting Nov. 2010
• Pre-Clinical
  — Rat sciatic nerve toxicology
  — More systemic GLP toxicology (Toxikon)
  — Sheep respiratory, neuromuscular and cardiovascular toxicology
  — Better PK assay in Children’s Hospital’s Clinical Laboratories
Rat Sciatic Blockade: Additional Prolongation by Epinephrine Added to NeoSTX-Bupivacaine (2012)

Green Arrows: Epinephrine effect: 6-fold prolongation of full block, 3-fold prolongation of half-block compared to Neo-Bup; > 10-fold compared to Bup
Excellent Hemodynamic Stability with Intravenous NeoSTX (Sheep)
Phase 1 Study under U.S. IND

- IND February 2013; Completed in 2014
- Phase 1 Trial: 66 subjects, NeoSTX-Bupivacaine
- Phase 1 Add-On Study: 18 subjects, NeoSTX-Bupivacaine-Epinephrine
- ASA October 2014 (Best Clinical Science Award)
- Anesthesiology October 2015 Cover, 2 Articles, and Editorial
Support

- TIDO
- BCH’s Technology-Development Fund
- Department of Anesthesiology, Perioperative and Pain Medicine under Paul Hickey’s leadership
- Sara Page Mayo’s and Richard Mayo’s Support and Endowment
A Small Molecule Derived from Cyanobacteria Holds Promise for Long-lasting Neural Blockade
Prolonged Skin Numbness and Pain Insensitivity with NeoSTX Combinations
Time to near-complete recovery of cutaneous mechanical thresholds in 10 and 30mcg NeoSTX-Saline, NeoSTX-Bup, and NeoSTX-Bup-Epi treatment groups.
NeoSTX Plasma Concentrations Versus Time

NeoSTX concentration = 30mcg+/−additives as labelled; Mean PK presented for each group
Potential Impact of Prolonged-Duration Local Anesthetics

- Greater safety with large doses/volumes
- Utility both intra-op and post-op
- OR work-flow - single-shot blocks more than catheters
- Wider spread of initial injectates versus infusions
- Reliability – if you prove a block is working pre-op, you should have 2 – 3 days of analgesia
- Impact in resource-limited countries
Conclusions

• Prolonged duration local anesthetics could possibly transform postoperative pain relief and accelerate recovery.
• Currently available formulations and additives have shown modest impact on analgesic durations and clinical outcomes.
Conclusions

• Neosaxitoxin is one possible candidate for achieving these goals, but it is in early-stage trials, and not yet close to approval.

• Drug development takes time and persistence.

• Our team’s progress to date was made possible by some unique resources and collaborations available at Boston Children’s Hospital