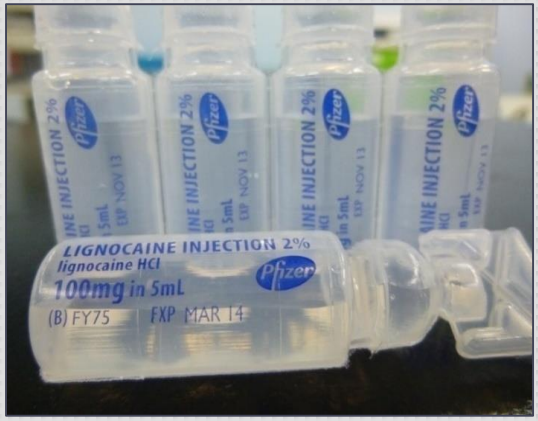
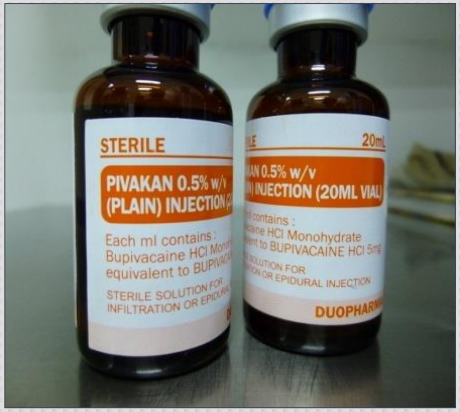
Towards Ideal Local Anaesthetics:

Where are we now



Dr Azrin Mohd Azidin
MBBS M Med (Anaes) A M
Dept of Anaesthesia and Intensive Care
Hospital Kuala Lumpur,
Malaysia

Local Anaesthetics



Content

- Review of Local Anaesthetics
- Ideal Properties
- Current Options
- Is it ideal?
- Issues on current use
- Clinical tips
- conclusion

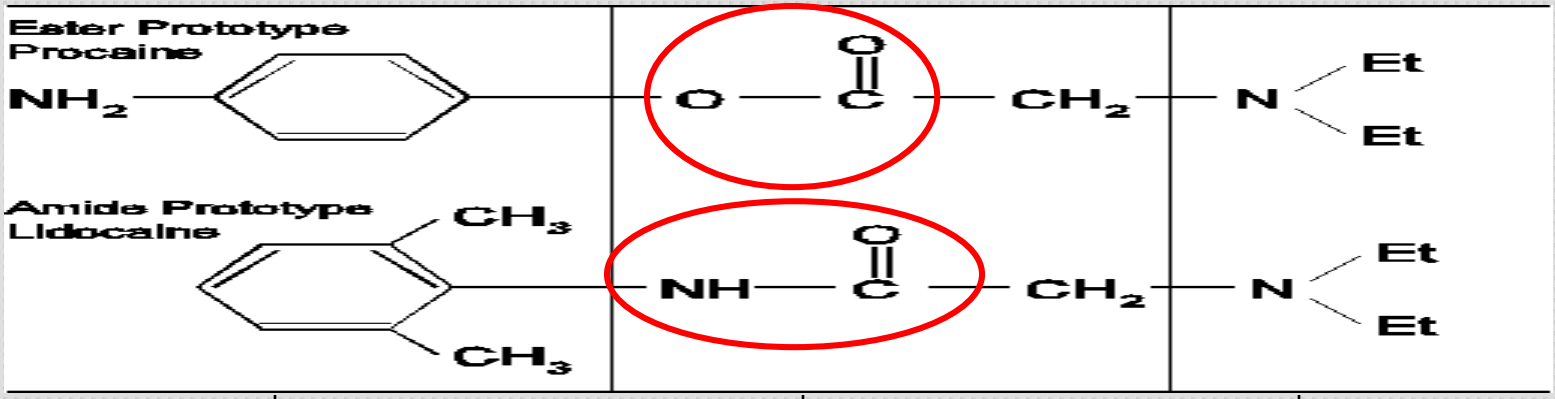
Definition

- Drugs that produce *reversible conduction blockade* of impulses along central & peripheral nerves
- Producing autonomic, sensory blockade & skeletal muscle paralysis in the area innervated by affected nerve

Classifications

Aminoesters	Aminoamides
Procaine	Prilocaine
Chloroprocaine	Etidocaine
Tetracaine	Mepivacaine
Amethocaine	Lignocaine
Cocaine	Bupivacaine
	Ropivacaine

Structure activity relationship



Unsaturated aromatic ring → Lipid solubility → Potency

Ester/Amide → Classification /Metabolism / Allergy

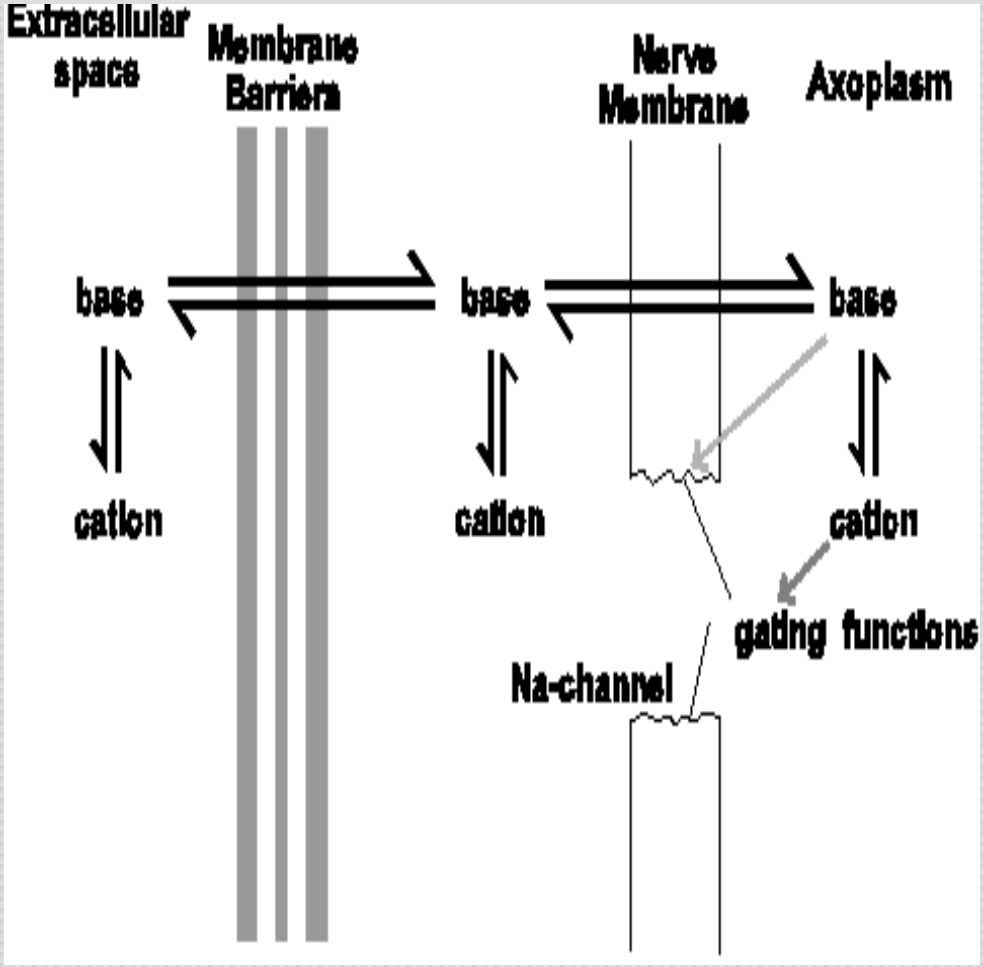
Tertiary amine → Water solubility

Common features

- Weak bases with pKa > 7.4: water insoluble
- Presented in solutions as acidic hydrochloric salts (pH 6): ionised cationic form water soluble
- In solution, exists as equilibrium mixture of free base & cationic form
- Body buffers raise pH & ↑free base which crosses axonal membrane
- Free base equilibrates with cationic form which acts on receptor

Mechanism of action

- Diffusion of the base across nerve sheath & nerve membrane
- Re-equilibration between the base & cationic forms in axoplasm
- Penetration of the cation & attachment to internal surface of the sodium channel
- Blockade of the sodium channel



What is ‘Ideal’

Exactly right for a particular purpose, situation or person

A conception of something in its absolute perfection

A person or thing conceived as embodying such a conception or standard and taken as a model for imitation

Ideal ?

Local Anaesthesic :	Frequency	Percent
Bupivacaine 0.25%	2	0.6%
Bupivacaine 0.5%	13	3.6%
I-bupivacaine 0.125%	2	0.6%
I-bupivacaine 0.25%	20	5.5%
I-bupivacaine 0.5%	49	13.5%
Ropivacaine 0.2%	50	13.8%
Ropivacaine 0.375%	96	26.4%
Ropivacaine 0.5%	60	16.5%
Ropivacaine 0.75%	71	19.6%
Total	363	100.0%

Hospital Kuala Lumpur ; Malaysian Registry in Regional Anaesthesia ; April – Dec 2012

Ideal ?

Time to motor power 3/5 :	Frequency	Percent
(i) < 6H	77	22.1%
(ii) 6-12 H	169	48.4%
(iii) 12-18 H	49	14.0%
(iv) 18-24 H	32	9.2%
(v) > 24 H	22	6.3%
Total	349	100.0%

Hospital Kuala Lumpur ; Malaysian Registry in Regional Anaesthesia ; April – Dec 2012

Ideal properties

Physicochemical	Pharmacokinetic	Pharmacodynamics
Easy to produce & economical	Ease of administration	High therapeutic index
Stability during storage	Rapid onset	No hypersensitivity reaction
Sterilisable by heat	Duration of action appropriate to use	Absence of toxicity on local tissues, liver, brain & other tissues
Free of additives	Clearance independent of hepatic/ renal function	Administration effective by topical, injection near nerve trunk & local infiltration
Soluble in water	No active/ toxic metabolites	Specificity: only nerve tissues affected

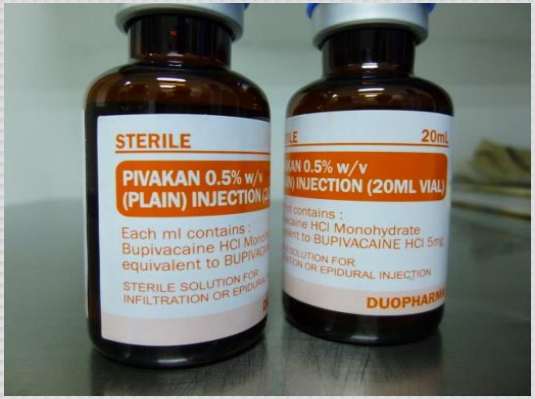
Ideal Properties for us…

- Easy and safe to use for multiple routes
- Reliable and Predictable
- Non-organ dependent metabolism /elimination
- Weakness sparing
- Propensity for differential blockade
- Favourable toxicity profile
- Appropriate
  - ONSET
  - DURATION OF ACTION


LIGNOCAINE INJECTION 2%
lignocaine HCl
100mg in 5mL
EXP MAR 14
Pfizer

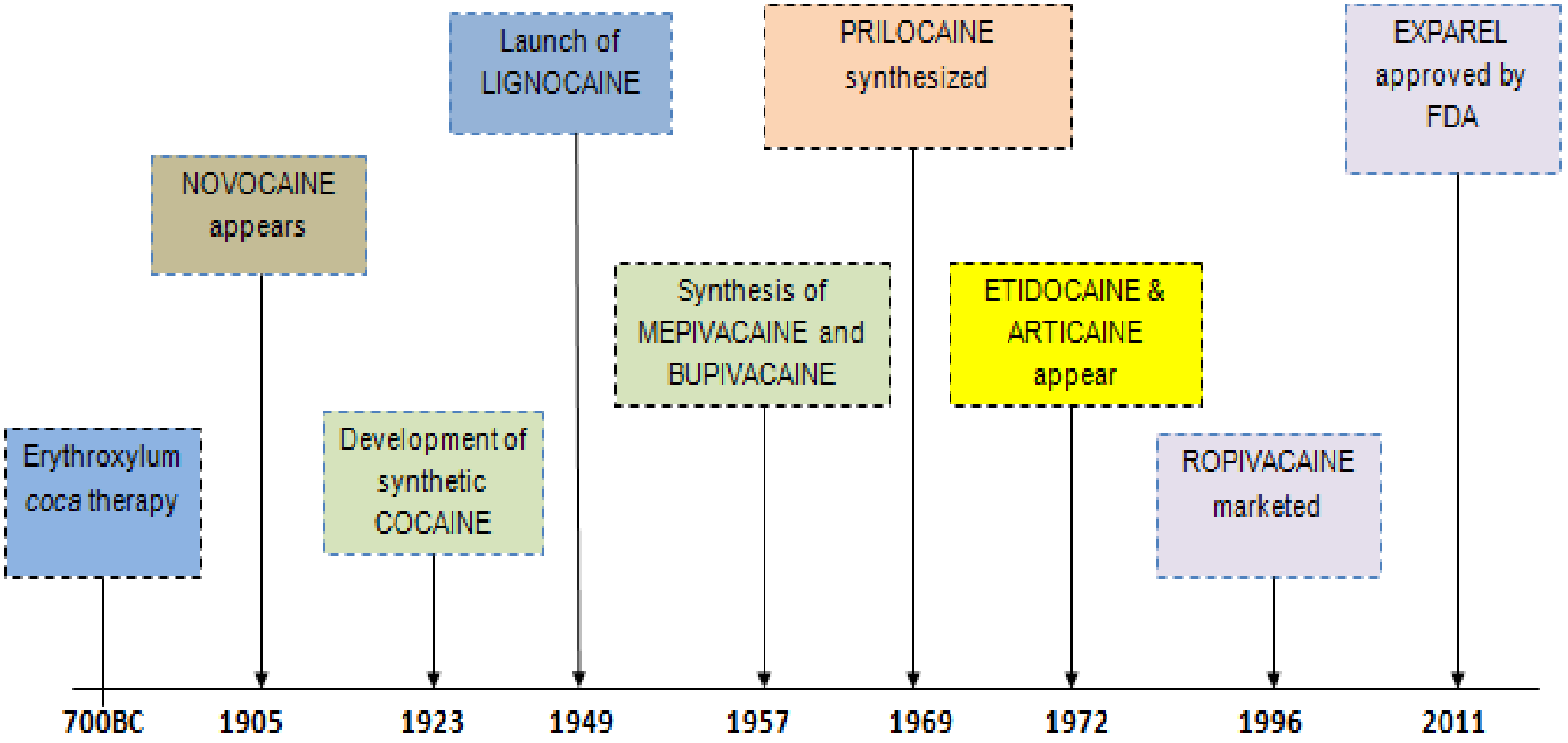

69 004 24.97
Naropin® 7.5 mg/ml
ropivacaine hydrochloride
20 ml injection
AstraZeneca
MAN. 02-2013
EXP. 01-2016
LOT LAFC
69 004 26.97
Naropin® 2 mg/ml
ropivacaine hydrochloride
20 ml injection
AstraZeneca
MAN. 06-2012
EXP. 05-2015
LOT CABB

Options ?

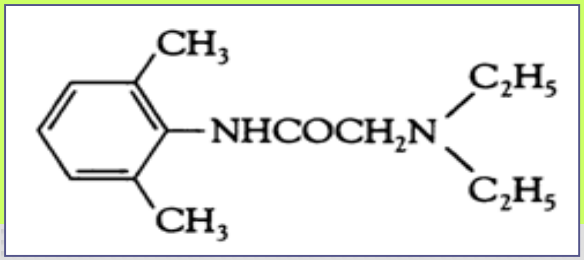

STERILE
PIVAKAN 0.5% w/v
(PLAIN) INJECTION
Each ml contains :
STERILE SOLUTION FOR
INFILTRATION OR EPIDURAL
20mL
INJECTION (20ML VIAL)
DUOPHARMA


CHIROCAINE 5.0 mg/ml
10 ml
CHIROCAINE 5.0 mg/ml

History of Local Anaesthesia

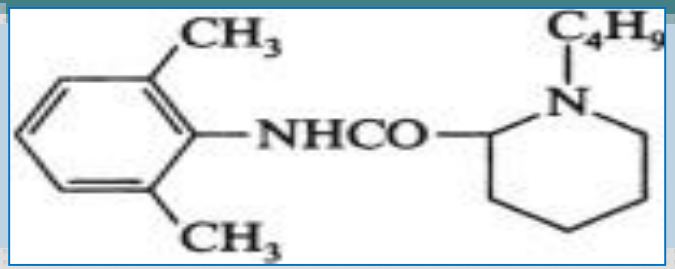


Lignocaine



- Structure: amide LA, derivative of diethylaminoacetic acid
- Presentation: clear aqueous solution (lignocaine hydrochloride)
  - ✓Plain: 0.5%, 1%, 2%
  - ✓With 1:200,000 (5µg/ml) adrenaline
  - ✓Gel 2%
  - ✓4% aqueous solution for topical application to pharynx, larynx, trachea
  - ✓10% spray for oral cavity & upper resp tract
- Recommended max dose 3mg/kg (7mg/kg with adrenaline)
- Clinical : acts within 5-20 min; duration 60-120 min depending on concentration & vasoconstrictor

Bupivacaine



- Structure: amide LA, pipecoloxylidide group, racemic
- Presentation: clear colourless, aqueous solution (bupivacaine hydrochloride)

✓ Plain: 0.25%, 0.5%, 0.75%

✓ With 1:200,000 (5µg/ml) adrenaline

✓ Heavy 0.5% with 80mg dextrose (SG 1.026)

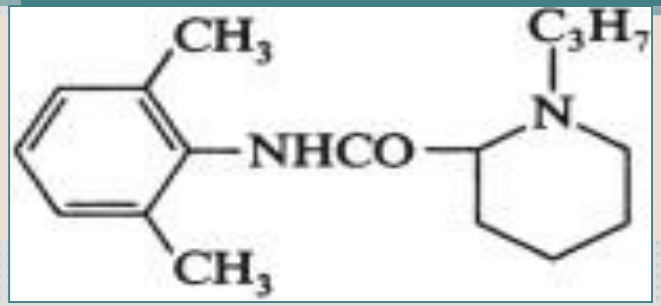
- Recommended max dose 2mg/kg (150mg + up to 50mg 2 hourly subsequently)
- Clinical : acts within 10-20 min& almost immediate with IT adm

✓ Duration of action 4-8 hrs

✓ 4x as potent as lignocaine

✓ Propensity for cardiotoxicity

Ropivacaine



- Structure: amide LA, pipecoloxylidide group, pure S-enantiomer
- Presentation: clear, colourless solution (ropivacaine hydrochloride) 0.2%, 0.75%, 1%
- Recommended max dose 3mg/kg
- Clinical :

✓ Sensory blockade similar in time course to that produced by bupivacaine

✓ Motor blockade slower in onset & shorter in duration

✓ Less cardiotoxic

✓ Intrinsic vasoconstrictor

Lignocaine

- Fast onset
- Short duration of action

- Inadequate post operative analgesia
- Toxicity profile
- Transient Neurological Syndrome

Bupivacaine

- Slow onset
- Intermediate to long duration of action (anaesthesia)

- ‘Inadequate’ duration for post operative analgesia
- Toxicity profile
- racemic

Levo- Bupivacaine

- Slow onset
- Intermediate to long duration of action (anaesthesia)
- Better cardiac toxicity profile

- ‘Inadequate’ duration for post operative analgesia
- Variable clinical experience (personal)
- Onset and block density

Ropivacaine

- Slow onset
- Intermediate to long duration of action (anaesthesia)
- Better cardiac toxicity profile
- Differential block

- ‘Inadequate’ duration for post operative analgesia
- Surgical anaesthesia may be inadequate.

Pain Mechanisms
Section Editor: Tony L. Yaksh/Quinn H. Hogan

Cytotoxicity of Local Anesthetics in Human Neuronal Cells

CONCLUSION: LAs can cause rapid cell death, which is primarily due to necrosis. Lidocaine and bupivacaine can trigger apoptosis with either increased time of exposure or increased concentration. These effects might be related to postoperative neurologic injury. Lidocaine, linked to the highest incidence of transient neurological symptoms, was not the most toxic LA, whereas bupivacaine, a drug causing a very low incidence of transient neurological symptoms, was the most toxic LA in our cell model. This suggests that cytotoxicity-induced nerve injury might have different mechanisms for different LAs and different target(s) other than neurons.

* Potency in causing neuronal cell death:

  Bupivacaine > ropivacaine > chloroprocaine > lignocaine > mepivacaine = procaine

* Bupivacaine and lignocaine kill all cells with increasing concentrations

(Anesth Analg 2009;108:997–1007)

The Neurotoxicity of Local Anesthetics on Growing Neurons: A Comparative Study of Lidocaine, Bupivacaine, Mepivacaine, and Ropivacaine

Radwan, Inas A. M. MD; Saito, Shigeru MD, PhD; Goto, Fumio MD, PhD

Effect of various LA on growth cone collapse;
Chick embryo; add LA various concentrations in media
Incubated up to 1 hour; washed and viewed through 40X phase contrast

Findings:

Lowest IC50- lignocaine, highest mepivacaine: bupi similar with ropi.

Lignocaine is potentially more neurotoxic than bupi at all clinically relevant concentrations.

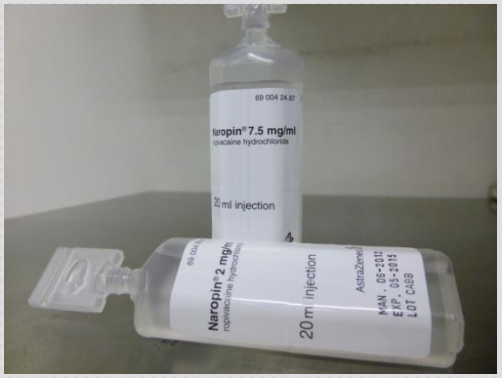
Anesth Analg. 2002;94:319-324

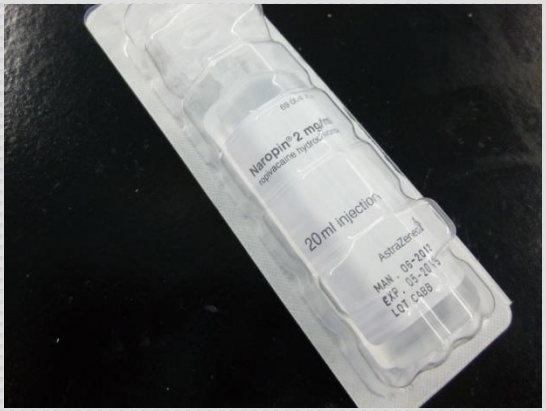
Considerations

- Blocks are procedure specific (anaesthesia v analgesia)
  - type of LA
  - Concentration v volume
- Adjuvants;
  - improve onset
  - prolongs analgesia
  - devoid of weakness
  - dose and reduction of toxicity
- Use of Catheter

Techniques to achieve ideal properties

- Additives/mixture
  - lignocaine
  - bicarbonate
- Adjuvants
  - adrenaline
  - clonidine
  - buprenorphine
  - dexamethasone
  - midazolam
- Catheter technique





Issues in adding lignocaine

- Common practice to hasten onset
- Variable dynamics after mixture
  - diffusion distance
  - dilution of intermediate to longer acting
- Occasional reports of toxicity due to
  - Excessive dosage
  - Additive mass of drug

Authority not in favour although acceptable

Addition of bicarbonate

- Only significance is only when using intermediate or long acting local anaesthetics
- Of no use with short acting

Adjuvants

- Clonidine, buprenorphine, dexamethasone and midazolam
- Issues whether effect seen is due to local effect or systemic
- Evidence only midazolam does have effect on action potential
- Potential of adjuvant toxicity. Dexamethasone

Neurotoxicity of Adjuvants Used in Perineural Anesthesia and Analgesia in Comparison With Ropivacaine

Brian A. Williams, MD, MBA,†‡ Karen A. Hough, AS, CVT, RLAT,*† Becky Y. K. Tsui, MPH,* James W. Ibinson, MD, PhD,*†‡ Michael S. Gold, PhD,*† and G. F. Gebhart, PhD*†*

Conclusions: Results with R reaffirm the need to identify ways to mitigate local anesthetic–induced neurotoxicity. While having no protective effect on R-induced neurotoxicity in vitro, future research with adjuvants should address if the C + B + D combination can enable reducing R concentrations needed to achieve equianalgesia (and/or provide equal or superior duration, in preclinical in vivo models).

(*Reg Anesth Pain Med* 2011;36: 225–230)

Catheter techniques

- Various contradicting studies on cost-effectiveness

  Candido et al (2010).
- Technically more challenging
- Secondary failure due to various reasons
- Issues on toxicity of LA and adjuvant due to concentration and time exposure

Continuous Peripheral Nerve Block Compared With Single-Injection Peripheral Nerve Block

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

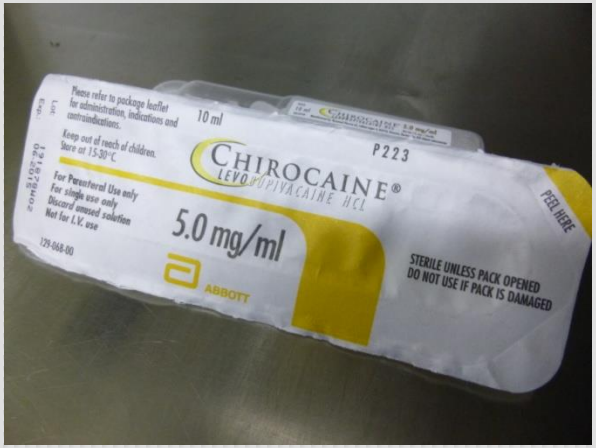
Ann E. Bingham, MD, Rochelle Fu, PhD,† Jean-Louis Horn, MD,† and Matthew S. Abrahams, MD†*

Methods: We conducted a systematic review and meta-analysis of all prospective, randomized trials comparing cPNBs with siPNBs. We used a validated systematic search strategy to identify potentially eligible studies. For studies meeting inclusion criteria, methodologic quality was scored independently by 2 reviewers. Data from the studies were abstracted and pooled for meta-analysis.

Conclusions: Compared with siPNBs, cPNBs were associated with improved pain control, decreased need for opioid analgesics, less nausea, and greater patient satisfaction. The effect of cPNBs on other clinically relevant outcomes, such as complications, long-term functional outcomes, or costs, remains unclear.

(*Reg Anesth Pain Med* 2012;37: 583–594)

Useful tips in practice



- Audit on own practice

  Malaysian Registry in Regional Anaesthesia (MyRRA)

- Procedure specific based on individual requirements
- Know LA dynamics

  concentration and volume

  additives

- Usual doses

  half the concentration for analgesia

  two-third strength for anaesthesia
- Guided techniques (US/NS/ Dual)
- If longer duration is required

  → use of catheter
- Early multi-modal analgesia

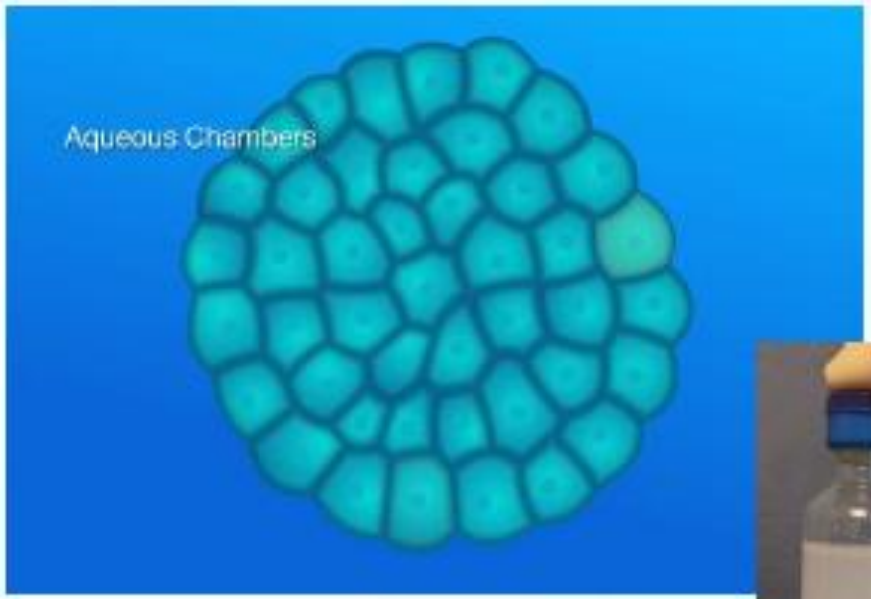
Duration of analgesia still too short….

- Development of controlled release mechanism from existing amino-amide LA from micro-particles, liposomes
- Controlled release reduce peak Cmax, and prolongs Tmax therefore improve duration and toxicity profile

Duration of analgesia still too short….

- New molecules with intrinsically prolonged action
- Mechanism similar to LA with improved pharmacokinetic/dynamic profile

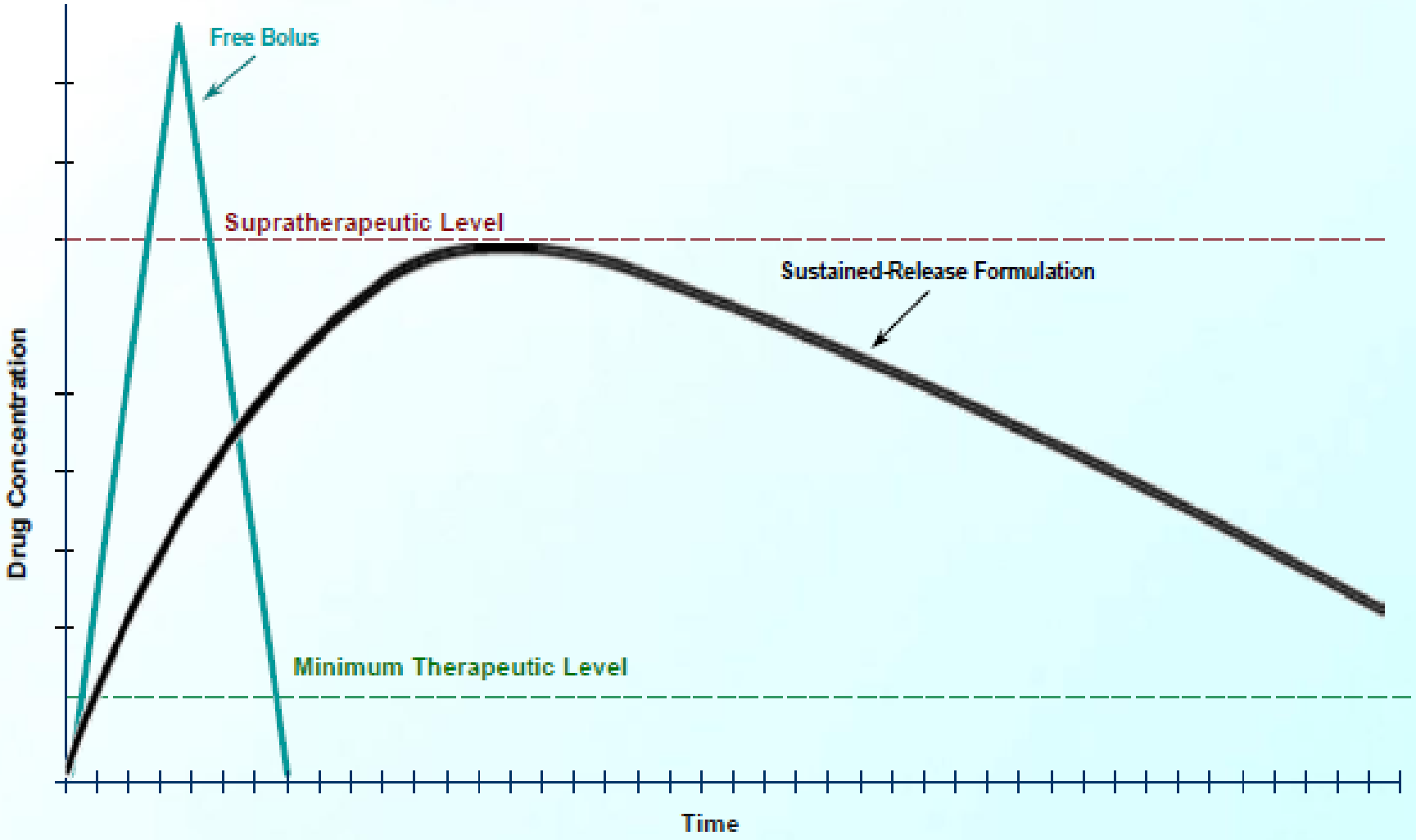
EXPAREL
DepoFoam® Release of bupivacaine



Liposomal Bupivacaine

- Depo- form with controlled release of Bupivacaine
- Unilamellar, Multilamellar Multi vesicular (MVL)
- contains hundreds of chambers resembling 'honeycomb-like matrix'.
- Naturally occurring or synthetic common Phospholipids (dierucoyl-PC and dipalmitoyl-PG), cholesterol and TG.
- >97% water phase to 1-3% lipids with high D/PL ratio of 1.8

Injectable Drug:
Sustained Release Profile



Pharmacokinetics..

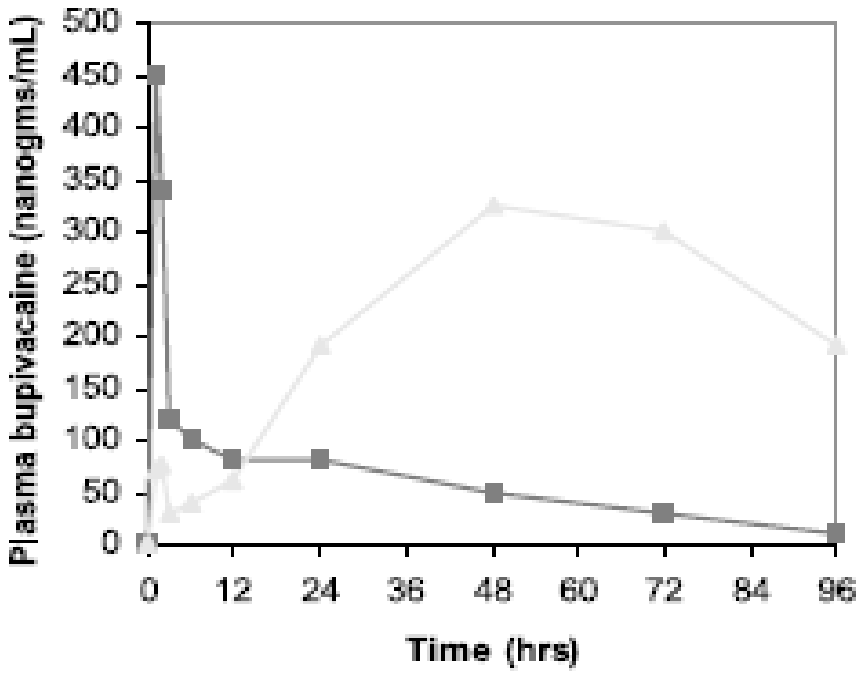
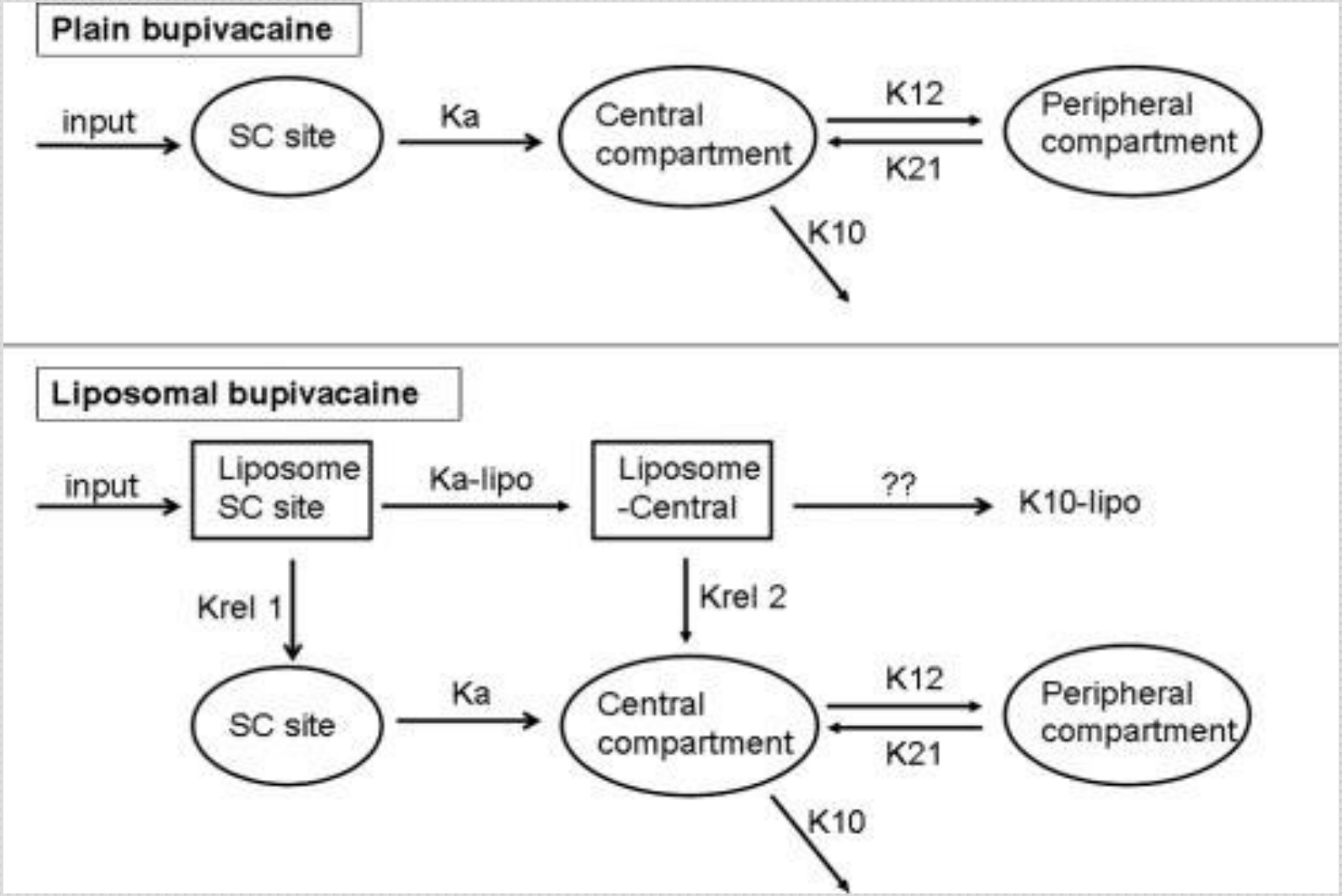


Fig 2. Plasma bupivacaine concentrations: aqueous versus microsphere subcutaneous injection in humans. Plasma concentrations of aqueous bupivacaine peak within an hour of injection and then rapidly decline. Bupivacaine microspheres show an initial rapid rise over the first 3 hours from free bupivacaine contained within the microsphere suspension and then peak well below aqueous bupivacaine. After a 3- to 12-hour plateau period, plasma bupivacaine concentration from microspheres gradually rises for 48 to 72 hours, and then declines. This pharmacokinetic profile explains the prolongation of neural blockade seen with microspheres.

Pharmacokinetics..



Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Liposomal bupivacaine: a review of a new bupivacaine formulation

This preparation increases the duration of local anesthetic action by slow release from the liposome and delays the peak plasma concentration when compared to plain bupivacaine administration. Liposomal bupivacaine has been approved by the US Food and Drug Administration for local infiltration for pain relief after bunionectomy and hemorrhoidectomy. Studies have shown it to be an effective tool for postoperative pain relief with opioid sparing effects and it has also been found to have an acceptable adverse effect profile. Its kinetics are favorable even in patients with moderate hepatic impairment, and it has been found not to delay wound healing after orthopedic surgery. More studies are needed to establish its safety and efficacy for use via intrathecal, epidural, or perineural routes.

Journal of Pain Research
13 August 2012

Research Article

The Safety of EXPAREL ® (Bupivacaine Liposome Injectable Suspension) Administered by Peripheral Nerve Block in Rabbits and Dogs

Brigitte M. Richard,[1] Paul Newton,[2] Laura R. Ott,[2] Dean Haan,[2] Abram N. Brubaker,[2] Phaedra I. Cole,[2] Paul E. Ross,[2] Marlon C. Rebelatto,[2] and Keith G. Nelson[2]

A sustained-release DepoFoam injection formulation of bupivacaine (EXPAREL, 15 mg/mL) is currently being investigated for postsurgical analgesia via peripheral nerve block (PNB). Single-dose toxicology studies of EXPAREL (9, 18, and 30 mg/kg), bupivacaine solution (Bsol, 9 mg/kg), and saline injected around the brachial plexus nerve bundle were performed in rabbits and dogs. The endpoints included clinical pathology, pharmacokinetics, and histopathology evaluation on Day 3 and Day 15 (2/sex/group/period). EXPAREL resulted in a nearly 4-fold lower C_{max} versus Bsol at the same dose. EXPAREL was well tolerated at doses up to 30 mg/kg. The only EXPAREL-related effect seen was minimal to mild granulomatous inflammation of adipose tissue around nerve roots (8 of 24 rabbits and 7 of 24 dogs) in the brachial plexus sites. The results indicate that EXPAREL was well tolerated in these models and did not produce nerve damage after PNB in rabbits and dogs.

Journal of Drug Delivery
Volume 2012, Article ID 962101, 10 pages

ANESTHESIA & ANALGESIA

High-Dose Bupivacaine Remotely Loaded into Multivesicular Liposomes Demonstrates Slow Drug Release Without Systemic Toxic Plasma Concentrations After Subcutaneous Administration in Humans

Elyad M. Davidson, MD,* Yechezkel Barenholz, PhD,† Rivka Cohen, PhD,† Simon Haroutiunian, MSc,*† Leonid Kagan, PhD,§ and Yehuda Ginosar, BSc, MBBS*

RESULTS: Eight subjects were studied. No subjective side effects of local anesthetics were observed. The maximal plasma concentration and the time to achieve maximal plasma concentration were assessed by modeling plasma concentration–time profiles. Maximal plasma concentration was not significantly different between groups (0.87 ± 0.45 μg/mL and 0.83 ± 0.34 μg/mL for plain and liposomal bupivacaine, respectively; P = not significant, 0.83). These values are well below the putative toxic plasma concentration of 2 to 4 μg/mL. Time to achieve maximal plasma concentration was 7-fold greater for the liposomal preparation (262 ± 149 minutes vs 37.5 ± 16 minutes, $P < 0.01$).

CONCLUSIONS: Peak plasma bupivacaine concentrations were not different in the 2 groups, despite a 4-fold increase in total bupivacaine dose administered in the novel liposomal preparation. The delayed elimination and prolonged redistribution of liposomal bupivacaine to plasma is compatible with the depot-related slow-release effect leading to the prolonged pharmacodynamic effect previously reported. (Anesth Analg 2010;110:1018–23)

The Pharmacokinetics and Pharmacodynamics of Liposome Bupivacaine Administered Via a Single Epidural Injection to Healthy Volunteers

Eugene R. Viscusi, MD, Keith A. Candiotti, MD,† Erol Onel, MD,‡ Michael Morren, RPh, MBA,§ and Guy L. Ludbrook, MBBS, PhD||*

Conclusions: Epidurally administered liposome bupivacaine 266 mg resulted in a longer duration of sensory blockade than liposome bupivacaine 89 or 155 mg or bupivacaine HCl 50 mg. Duration of motor blockade was shorter with liposome bupivacaine 266 mg versus bupivacaine HCl.

(*Reg Anesth Pain Med* 2012;37: 616–622)

EDITORIAL

Will Conventional Local Anesthetics Soon Be Replaced by Neurotoxins?

John F. Butterworth, IV, MD

In summary, as intriguing as these results are, Rodriguez-Navarro and colleagues[5] have merely demonstrated that neosaxitoxin may be capable of producing the longest persisting local infiltration block in medical history. We have a long way to travel on this scientific road before local anesthetics join the

Regional Anesthesia and Pain Medicine • Volume 36, Number 2, March-April 2011

Neosaxitoxin as a Local Anesthetic

Preliminary Observations from a First Human Trial

Alberto J. Rodriguez-Navarro, M.D., Nestor Lagos, Ph.D.,† Marcelo Lagos, M.D.,‡ Italo Braghetto, M.D.,§ Attila Csendes, M.D.,§ James Hamilton, M.D.,‖ Cristian Figueroa, M.D.,‡ Dominique Truan, M.Sc.,‡ Carlos Garcia, M.Sc.,‡ Andres Rojas, M.D.,‡ Veronica Iglesias, M.Sc.,# Luis Brunet, M.D.,** Francisco Alvarez, M.D.††*

Results: **For all the patients, effective and complete blocking of the evaluated parameters was obtained. As the blocking began to revert gradually, heat pain was the first to return to normal values after 3 h. Cold pain was the longest sensation abolished, achieving 24 h of blockade. The toxin was undetected in blood and urine samples. No adverse reactions to neosaxitoxin were detected.**

Conclusions: **Neosaxitoxin showed an effective local anesthetic effect when injected in the subcutaneous plane. The efficacy of a 50-μg dose of neosaxitoxin was shown. This is the first report of neosaxitoxin as a local anesthetic in a human trial.**

Anesthesiology 2007; 106:339–45

Comparison of Neosaxitoxin Versus Bupivacaine via Port Infiltration for Postoperative Analgesia Following Laparoscopic Cholecystectomy

A Randomized, Double-Blind Trial

Alberto J. Rodríguez-Navarro, MD,†‡ Charles B. Berde, MD, PhD,§|| Gonzalo Wiedmaier, MD,* Andres Mercado, MD,* Carlos Garcia, MSc,‡ Veronica Iglesias, PhD,¶ and David Zurakowski, PhD§||*

Conclusions: NeoSTX shows promise as a long-acting local anesthetic. Future studies will examine dose response, combination formulations, and safety with dose escalation.

(*Reg Anesth Pain Med* 2011;36: 103–109)

Neosaxitoxin- Why can it work?

- Blocks sodium channels (Site 1 Toxins)
- does not block Na_v 1.5 myocyte channels
- does not cross blood brain barrier:

  low potential for CNS toxicity (seizures)
- Potential in 1st human trial in LIA laparoscopic cholecystectomy

Why can't it work… now…

- Require dose/volume-finding studies
- Human trial on laparoscopic cholecystectomy
- Mild to moderate pain
- Only LI/SC infiltration:

  requires further studies on central/ perineural route

Conclusion

- Is there any ideal LA?
  - No
- Knowing your LA
- Making it ideal for your practice
- Liposomal Bupivacaine?
- Neosaxitoxin?

-> wait for more evidence

Thank You