Liposomal bupivacaine: a review of a new bupivacaine formulation

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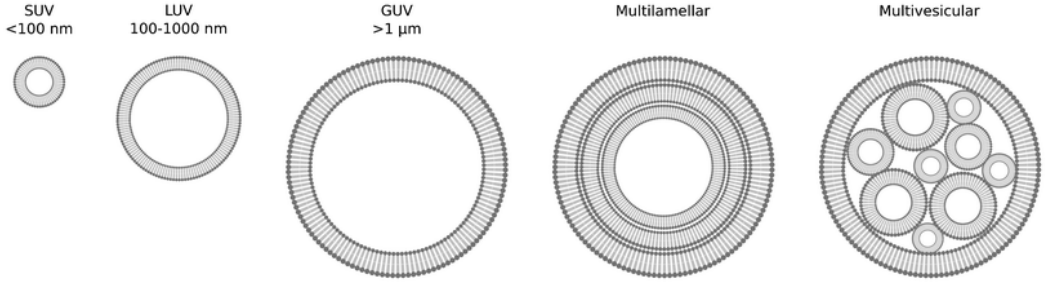
Introduction

- In a post-operative setting, pain is an undesirable side effect of surgery
- Adequate post-operative pain control has noted effects of improved cardiac, respiratory and gastrointestinal function, fewer thromboembolic complications, reduced post-surgical chronic pain, reduced mortality and reduced health care costs
- Opioids are heavily relied on for achieving peri and post-operative analgesia; however numerous side effects including nausea, vomiting, respiratory depression, tolerance and the development of hyperalgesia limit their use.
- As a part of a multimodal regimen, local anesthetics are increasingly used perioperatively in order to reduce opioid requirements. Use of local anesthetics for post-operative pain control is limited by duration of action. For example, average duration of block with 0.5% bupivacaine or ropivacaine is 8-12 hours. Catheters may be placed to allow infusion and increase the duration of analgesia; however these require additional training, costs and maintenance and carry risks.
- Development of novel, long-acting local anesthetics such as liposomal bupivacaine are potential means of offering safe, long-lasting pain relief.

Liposomal Bupivacaine

- Liposomes consist of phospholipid bilayer encompassing an aqueous core. May be unilamellar (ULV), multilamellar (MLV), or multivesicular (MVV).



- MVV liposomes consist of non-concentric lipid bilayers. The non-concentric nature of MVL allows for several qualities which are desirable for a drug delivery system.
    - MVL vesicles contain water soluble drugs in the core and lipid soluble drugs in the membrane
    - Non-concentric nature allows sustained, stable drug release pattern from an aqueous core that is not possible with the other vesicle types. Breach of the external MVL layer allows drug release, and release of drug from internal vesicles leads to redistribution of the drug without further drug release into the body.
    - Multivesicular structure prevents rearrangement and release of drugs by internal fusion and division
- Liposomal bupivacaine (LB) contains vesicles of bupivacaine loaded in the aqueous cores with DepoFoam technology (Pacira Pharmaceuticals Inc). This mimics a honeycomb srcture of several internal aqueous chambers containing bupivacaine.

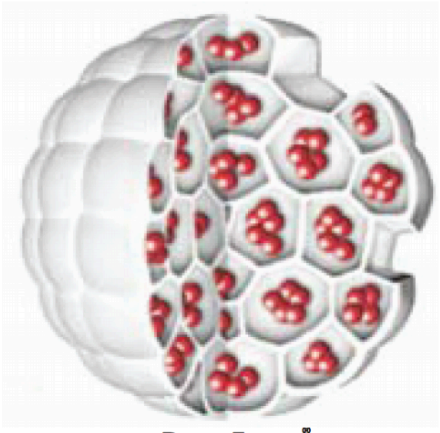


Figure 2 Cross-sectional diagram of DepoFoam containing bupivacaine. Image supplied courtesy of Pacira Pharmaceuticals, Inc, 5 Sylvan Way, Parsippany, NJ 07054.

Pharmacodynamics

- Bupivacaine is an amide local anesthetics, which inactivates voltage-dependent sodium channels. At normal tissue pH, 15% is present in uncharged form (pKa 8.1) which cross the cell membrane, become polarized and bind and inactive the sodium channels.
- The slow release of bupivacaine from its binding site leads to a long duration of action versus lidocaine

Pharmacokinetics

- The pharmacokinetics of LB has been studied in animal and human models
- In animals, Richard et al found C_{max} for LB to be dose dependent and much lower than plain bupivacaine (for LB doses of 9, 18, 30 mg/kig versus 9 mg/kg plain bupivacaine). Plasma bupivacaine concentration in the plain bupivacaine group peaked earlier compared to LB group: 1 h versus 12.5±8.06, 7.0±11.3, 30.3±22.5 hours for the three doses of LB, respectively. Plasma concentrations were detectable in the majority of dogs who received LB 9 mg/kg over 96-hour period.
- In humans, Davidson et al found no difference in C_{max} for subcutaneous injections of 2% LB (20 mL) versus 0.5% plain bupivacaine (20mL), despite a 4-fold increase in dose and 9.8-fold increase in terminal half-life of the LB group. T_{max} increased 7-fold in LB group, which was attributed to the slow release of liposomal bupivacaine.
- Bupivacaine is metabolized primarily by the liver by glucuronide conjugation and hepatic N-dealkylation into pipecolylxylidine. Pipecolylxylidine is hydroxylated into glucuronide conjugates. In a study in patients with moderate hepatic impairment, Onel et al found higher levels of bupivacaine and pipecolylxylidine versus patients with normal hepatic function; however, the concentration time plots were similar in both groups and dose adjustment were deemed unnecessary as per FDA guidelines.

Efficacy in Postoperative Pain

- FDA has approved single dose LB wound infiltration for post-operative pain relief after hemorrhoidectomy and bunionectomy
- A multicenter, RCT by Gorfine et al for patients receiving hemorrhoidectomy found that in patients receiving either 300 mg LB or placebo 0.9% NaCl, pains scores were markedly lower in the extended release LB group. Primary outcome measure involved a cumulative pain score over first 72 hours, and secondary outcome measure involved assessing need for opioid rescue medications, total opioids consumed and time to first use of rescue medications. In the LB group, 59% of patients were opioid free at 12 hours versus 15% in the placebo group, the total amount of opioid consume was lower in the LB group (22.3 mg vs 29.1 mg), and the median time to first opioid use was longer (14.3 h vs 1.2 h).
- A multicenter RCT by Golf et al examined the extended release LB group to placebo in patients undergoing bunionectomy. Rescue analgesia was 5mg oxycodone/325 mg acetaminophen. Researchers found markedly reduced pain intensity scores at 24 and 36 hours post injection in LB group versus placebo, with no difference at 48 hours. Fewer patients in the LB group required rescue analgesia through 24 hours and time to first opioid use was longer.
- Additional studies:

Table 1 Studies comparing the efficacy of MVL bupivacaine versus placebo or bupivacaine HCl

Author	Type of study	Comparison	Surgery	Primary outcome	Results
Gorfine et al[27]	RCT	300 mg DepoFoam bupivacaine compared with placebo	Hemorrhoidectomy	AUC_{0-72} of NRS pain intensity scores	Least square mean (SE) AUC_{0-72} 141.8 (10.7) in the DepoFoam bupivacaine (n = 94) group compared to 202.5 (10.7) in placebo (n = 93). $P < 0.0001$.
Golf et al[28]	RCT	120 mg DepoFoam bupivacaine compared with placebo	Bunionectomy	AUC_{0-24} of NRS pain intensity scores	Least square mean (SE) AUC_{0-24} 123.936 (4.4854) in DepoFoam bupivacaine group (n = 93) compared to 146.233 (4.5869) in placebo (n = 92). $P < 0.0005$. 95% CI of difference between DepoFoam bupivacaine vs placebo −34.799 to −9.794.
Smoot et al[29]	RCT	600 mg DepoFoam bupivacaine compared with 200 mg bupivacaine HCl with epinephrine 1:200,000	Submuscular augmentation mammoplasty	AUC_{0-72} of NRS-A pain intensity scores	Mean (SE) AUC_{0-72} 441.5 (23.6) in DepoFoam bupivacaine group (n = 66) and 468.2 (23.0) in bupivacaine HCl group (n = 70). $P = 0.3999$.
Bramlett et al[30]	RCT	Bupivacaine HCl 150 mg (0.5%) with epinephrine 1:200,000 compared with four doses of DepoFoam bupivacaine (133, 266, 399, and 532 mg)	Total knee arthroplasty	AUC_{0-96} of NRS-A pain intensity scores	Mean (SD) 20.7 (5.4), 19.5 (5.3), 18.8 (5.3), and 19.1 (4.4) in DepoFoam bupivacaine 133 mg, 266 mg, 399 mg, and 532 mg groups (n = 25, 24, 26, and 21, respectively) and 20.4 (3.9) in the bupivacaine HCl group (n = 30). P value >0.05 in each DepoFoam bupivacaine group compared to bupivacaine HCl group.

Abbreviations: AUC, area under the curve; MVL, multivesicular liposomes; NRS, numerical rating score; NOS, not otherwise specified; NRS-A, numerical rating score with activity; RCT, randomized clinical trial; SD, standard deviation; SE, standared error.

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Safety

- Most common side effects of liposomal bupivacaine in clinical trials included nausea, vomiting, constipation, pyrexia, dizziness and headache. More serious adverse effects may affect the cardiovascular and central nervous system. Bupivacaine is more cardiotoxic than lidocaine, due to its greater ability to produce cardiac conduction block.
- Bupivacaine also has potential for mytotoxicity, which may be related to calcium-induced muscle cell apoptosis (programmed cell death). Myotoxicity of bupivacaine is most likely after retrobulbar and peribulbar blocks (0.25% incidence of diplopia)
- Bergese et al examined the cardiac safety of LB (doses 150, 300, 450, 600 mg) versus plain bupivacaine and found no significant differences in baseline QRS or QTc duration in the two groups. No changes in baseline heart rate and PR interval were also found.
- Concomitant use of DepoFoam with another local anesthetic may increase the release of bupivacaine and therefore should not be performed. Also, DepoFoam should not come into contact with chlorhexidine or povidine iodine or other antiseptics as it may disrupt the lipid layers and lead to uncontrolled release of bupivacaine.

Summary

- A novel method of encapsulating local anesthetic within carrier molecules has been developed in order to increase the duration of anesthesia
- Bupivacaine loaded in multivesicular liposomes (liposomal bupivacaine) has been recently approved by the US Food and Drug Administration for local infiltration for pain management after bunionectomy and hemorrhoidectomy
- Studies reveal it to be effective in relieving postoperative pain and may enable reduced opioid doses without loss of analgesic efficacy
- Adverse effects profile appears acceptable, and appear safe to use even in patients with moderately impaired liver function. LB has not been shown to be more toxic than plain bupivacaine and does not appear to have different cardiac effects than plain bupivacaine.
- Additional research is required to establish safety and efficacy for use via intrathecal, epidural and perineural routes as well as applications to dentistry. More powerful clinical trials are needed to demonstrate the increase analgesic efficacy and cost effectiveness of LB compared to plain bupivacaine.
- Liposomal bupivacaine administered locally appears to be a valuable, opioid sparing method of providing post-operative pain control while reducing costs and complications related to catheters and infusion pumps

Reference

Chahar, Praveen, and Kenneth C. Cummings III. "Liposomal bupivacaine: a review of a new bupivacaine formulation." *Journal of pain research* 5 (2012): 257.