Liposomal Bupivacaine

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Objectives
- Describe the vehicle, prescribing instructions, and pharmacokinetics of liposomal bupivacaine
- Identify the potential local and systemic toxicities associated with liposomal bupivacaine administration
- Review the available literature describing liposomal bupivacaine local infiltration for postoperative analgesia
- Review the (limited) literature describing perineural and neuraxial administration of liposomal bupivacaine

Disclosures
I have no commercial conflicts of interest

Perineural Catheters
1. Technically more difficult
2. Expensive
3. Inflammation (3-4%)
4. Infection (<1%)
5. Catheter dislodgement
6. Catheter knotting / breaking
7. Intravascular migration
8. Myonecrosis
9. Hematoma

Liposomal Bupivacaine (Exparel®)
- DepoFoam®
  - Multivesicular spherical lipid particles in a honeycomb formation
  - Aqueous center containing encapsulated drug
  - Same delivery system as DepoDur®
- Approved only for surgical site infiltration
  - Contraindicated for paracervical blocks
  - Phase 2 and 3 trials for peripheral nerve blocks
Liposomal Bupivacaine

Prescribing Information

(Pacira Pharmaceuticals, Inc.)

- 20 ml, single use vial, 1.33% (13.3 mg/ml)
- Refrigerated
  - May be stored unopened at room temperature for up to 30 days
- May be maximally diluted to 0.89 mg/ml
- Must be used within 4 hours of opening
- Minimum 25 gauge needle
- $285 per 20 ml vial (AWS)
- Similar physical appearance to propofol.

Liposomal Bupivacaine Compatibility

A review of the compatibility of liposome bupivacaine with other drug products and commonly used implant materials.

Liposome bupivacaine had clinically meaningful interactions with other local anesthetics, including lidocaine, ropivacaine, mepivacaine, or bupivacaine HCl (at liposome bupivacaine to bupivacaine HCl ratios < 2:1), which resulted in substantial displacement and release of free bupivacaine from liposomes .

Liposome bupivacaine may be locally administered after ≥ 20 minutes following local administration of lidocaine, ropivacaine, or mepivacaine.

The administration of EXPAREL® may follow the administration of lidocaine after a delay of 20 minutes or more. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL®.
Liposomal Bupivacaine Systemic Toxicity

Toxicity of Bupivacaine Encapsulated into Liposomes and Injected Intravenously: Comparison with Plain Solutions

- Slow infusion of liposomal bupivacaine titrated to toxicity required larger doses
- No bolus, no temporal evaluation, no attempts at resuscitation
- Not using proprietary DepoFoam®

Neurologic / Cardiovascular Toxicity

Liposomal Bupivacaine Local Toxicity

Research Article

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

In conclusion, a single administration of EXPAREL was demonstrated to be safe by peripheral nerve block in rabbits and dogs when tested in comparison with bupivacaine HC3 and saline. EXPAREL did not cause overt irritation or local tissue damage even when injected at high dose or concentration around the brachial plexus nerve bundle.

Bupivacaine did not impact directly on neural tissue, and the findings of granulomatous inflammation were more consistent with a nonspecific foreign—body type reaction most likely mediated by the DepoFoam particles.

Myotoxicity

Chondrotoxicity appears to be a much more salient problem in intra-articular usage of EXPAREL.

Table V. Total bupivacaine concentration in wound drainage fluid over 12 hours with bupivacaine HCl or liposome bupivaca ine. Values are means.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total Bupivacaine Concentration in Wound Drainage Fluid Over 12 h, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine HCl 150 mg</td>
<td>2.3</td>
</tr>
<tr>
<td>Liposome bupivacaine 133 mg</td>
<td>0.6</td>
</tr>
<tr>
<td>266 mg</td>
<td>4.9</td>
</tr>
<tr>
<td>399 mg</td>
<td>5.8</td>
</tr>
<tr>
<td>532 mg</td>
<td>5.5</td>
</tr>
</tbody>
</table>


Caution...

The Food and Drug Administration (FDA) has approved liposomal bupivacaine for local infiltration, but has not granted approval for the use of liposomal bupivacaine in peripheral and neuraxial nerve blocks. Until FDA approval is granted, liposomal bupivacaine in regional anesthesia should be considered investigational. The risks and benefits of liposomal bupivacaine in peripheral and neuraxial nerve blocks need further investigation.

- Not approved for:
  - age < 18 years old
  - pregnant patients (Category C)
  - breastfeeding mothers

Best Practice & Research Clinical Anaesthesiology 28 (2014) 15–27
The effect of liposomal bupivacaine injection during total hip arthroplasty: a controlled cohort study  
*BMC Musculoskeletal Disorders 2014, 15:310*

- Reduced morphine use in first 24 hours  
  - (53 vs. 24 mg)  
- Reduced LOS  
  - (2.47 vs. 1.93 days, p=0.05)  
- Controls via retrospective chart review  
- Significant bias toward hip resurfacing in control group (33% vs 11%)

Liposomal bupivacaine infiltration into the transversus abdominis plane for postsurgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients  
*Journal of Pain Research 2014:7 477–482*

- No control group  
- 77% required supplemental analgesia  
- No adverse events  
- 10 day follow-up by surgeons

Medial and Lateral Pectoral Nerve Block with Liposomal Bupivacaine for the Management of Postsurgical Pain after Submuscular Breast Augmentation  
*Plast Reconstr Surg Glob Open 2014:2 e282*

A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty  
*Knee 19 (2012) 530–536*

- No control group  
- 77% required supplemental analgesia  
- No adverse events  
- 10 day follow-up by surgeons

Extended pain relief trial utilizing infiltration of Exparel®<sup>®</sup>, a long-acting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy  
*Journal of Pain Research 2012:5 567–572*
Liposomal Bupivacaine Versus Traditional Periarticular Injection for Pain Control After Total Knee Arthroplasty

Deren T. Bagdy, MD, Phillip H. Ireland, MD, R. Michael Meneghelini, MD
Department of Orthopaedic Surgery, Indiana University Health Physicians, Indiana University School of Medicine, Indianapolis, Indiana

The Journal of Arthroplasty 29 (2014) 1687–1690

Table 2
Patient Drug Outcome Measures.

<table>
<thead>
<tr>
<th>Liposomal Bupivacaine</th>
<th>Propivacaine Injection</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time until 1st opoid (min) Self-Rated Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 24 h</td>
<td>1.94 ± 2.10</td>
<td>1.93 ± 2.14</td>
</tr>
<tr>
<td>Remaining Stay</td>
<td>4.89 ± 1.35</td>
<td>4.38 ± 1.60</td>
</tr>
<tr>
<td>Final</td>
<td>4.11 ± 1.86</td>
<td>3.63 ± 3.09</td>
</tr>
<tr>
<td>Opiate Usage (Mdag)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 24 h</td>
<td>6.21 ± 18.30</td>
<td>13.75 ± 15.42</td>
</tr>
<tr>
<td>Remaining Stay</td>
<td>79.40 ± 62.97</td>
<td>55.53 ± 65.40</td>
</tr>
<tr>
<td>Anti-Emeric Doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 24 h</td>
<td>0.72 ± 1.14</td>
<td>0.47 ± 0.85</td>
</tr>
<tr>
<td>Remaining Stay</td>
<td>1.03 ± 1.85</td>
<td>0.81 ± 1.55</td>
</tr>
<tr>
<td>Naloxone Doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 24 h</td>
<td>0.03 ± 0.25</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Remaining Stay</td>
<td>0.00 ± 0.00</td>
<td>0.03 ± 0.15</td>
</tr>
</tbody>
</table>

 Eq = Intravenous Morphine Equivalents.

The Use of Exparel (Liposomal Bupivacaine) to Manage Postoperative Pain in Unilateral Total Knee Arthroplasty Patients

Jonathan W. Sutliffe, MD, David J. Kints, MD, Nathan T. Barnes, PA-C, Brittany R. Auez, BSN, BS, CBNN
Department of Orthopaedic Surgery/Indiana University Health, Indianapolis, Indiana
The Journal of Arthroplasty xxx (2014) xxx–xxx

The Journal of Arthroplasty xxx (2014) xxx–xxx

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The Journal of Arthroplasty xxx (2014) xxx–xxx

Femoral Block

Fig. 7. Comparison of average analgesia for patients treated with FNB and Exparel. * indicates significant difference.

Fig. 8. Cumulative total of discharge comparing patients treated by FNB and Exparel. * indicates significant difference.
Based on this case, we speculate that other types of rib pathology—for example, traumatic rib fractures—may also be amenable to palliation with intercostal nerve block with liposomal bupivacaine.