Determination of Local Concentrations of Bupivacaine Using Microdialysis Techniques

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Acknowledgements

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Goals

- Investigation of new sampling technique for the large and growing class of locally-acting products
- Development of ‘bioequivalence methods’ of ‘complex products such as…liposomes’
Multimodal analgesia

- Synergistic effect
- Greater efficacy
- Lower doses of each respective agent
- Earlier transition to outpatient setting
- Decreased costs of care
Extended release local anesthetics

- Long duration of analgesic action
- Reduced requirement for postoperative opioids
- Minimal systemic exposure
- Quicker return to normal bodily function and ambulation
FDA approved drugs for postsurgical pain management

- EXPAREL™, a 72-hour, extended-release bupivacaine liposome injectable suspension
- DepoDur™, a single-dose 48 hour extended-release epidural morphine sulfate liposomes
EXPAREL™: structure of a DepoFoam particle

The median diameter of the liposome particles ranges from 24 to 31 μm

Bupivacaine particles

Multivesicular liposomes (MVL)
EXPAREL™: as a model system

- The MVL are suspended in a 0.9% sodium chloride solution

- Each vial contains
  - Bupivacaine 13.3 mg/mL
  - Inactive ingredients
    - Cholesterol
    - Tricaprylin (neutral lipid)
    - 1, 2-Dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), (amphipathic lipid)
    - 1, 2-Dierucoylphosphatidylcholine (DEPC), (amphipathic lipid)

- The pH 5.8 to 7.4
Local monitoring methods

- Monitoring clinical bioequivalence for site-specific products are needed as these complex products advance.

- Ensure generic products meet the performance of innovator brand products.
Generics

- A generic drug must contain the same active ingredients as the innovator product

- Generics are identical or within an acceptable bioequivalent range to the brand drug with respect to PK/PD
Project outline

- Quantify the kinetics of elimination of drug after EXPAREL™ is administered
  - Utilizing microdialysis sampling
    - Monitor the extracellular concentration in the tissue
    - Near the site of administration

- Recommend bioequivalence methods for locally-acting, long acting analgesics
Sampling techniques

- In vitro sampling
- In vivo sampling
  - Blood
  - Tissue
  - Urine
  - Microdialysis
Microdialysis sampling

- Extracellular fluid sampling
- Concentration gradient
- Tissue specific sampling
- Minimal perturbation
- Protein-free samples
Experimental design

1. Develop microdialysis probe implantation procedures both in the hind leg muscle and in the subcutaneous space of conscious, freely-moving rats

2. Evaluate the time course of local concentration of bupivacaine following IM or SC administration of EXPAREL™ and two ‘generics’ formulated in our lab

3. Fit local drug elimination rate data to models and propose bioequivalence standards
**In-vitro Extraction Efficiency**

### Delivery

- Perfusate: Bupivacaine + Antipyrine
- Saline solution in v-vial and stirred continuously and kept at 37°C

### Recovery

- Perfusate: Antipyrine 2 µg/mL
- Bupivacaine put in bath containing saline solution, stirred continuously and kept at 37°C
Microdialysis

**EE** = \( \frac{C_{\text{perfusate}} - C_{\text{dialysate}}}{C_{\text{perfusate}} - C_{\text{sample}}} \)

**Recovery**

\[ EE_R = \frac{C_d}{C_s} \]

**Delivery**

\[ EE_D = \frac{C_p - C_d}{C_p} \]
In vitro extraction efficiency

- The EE$_R$ is not statistically different than EE$_D$ in vitro
- Bupivacaine is not interacting with the membrane materials

<table>
<thead>
<tr>
<th>Extraction Efficiency (EE)**</th>
<th>Antipyrine (Internal standard)</th>
<th>Bupivacaine HCl</th>
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<tbody>
<tr>
<td><strong>Delivery (EE$_D$)</strong></td>
<td>64 ± 1 (2%)</td>
<td>64 ± 1 (2%)</td>
</tr>
<tr>
<td><strong>Recovery (EE$_R$)</strong></td>
<td>65 ± 3 (5%)</td>
<td>61 ± 3 (5%)</td>
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</table>

**EE% ± SD (RSD)
Monitoring % free bupivacaine 
in vitro

% Free Bupivacaine in dialysate

Time (Hour)

Bupivacaine HCl
Exparel
Generic I

Generic I: contains DPPC instead of the highly expensive DEPC
**In vivo experimental timeline**

- Bupivacaine administration (IM)
- Bupivacaine administration (SC)
- Animal euthanized
  - Histologic examination
- Monitor pharmacokinetics of bupivacaine
- In vivo determination of EE_D for bupivacaine (20µg/mL) over 4 h
- Implant microdialysis probe (SC)
- Implant microdialysis probe (IM)
Microdialysis implantation experiment

Probe tubing

Site of administration (1 cm from the membrane)

Microdialysis membrane (5 mm)
Awake *in vivo* microdialysis
Microdialysis sampling technique
Microdialysis sampling versus blood sampling

- Over 10 times increase in the concentration of bupivacaine by using microdialysis sampling

K Candiotti, E Haas - Anesthesiology News, 2012
Conclusion

- There was no significant difference between *in vitro* recovery and delivery extraction efficiency (EE) for bupivacaine HCl indicating the viability of microdialysis sampling.

- Formulation of two generics with encapsulation efficiency of ~50%.

- Successful development of microdialysis probe implantation method for long term monitoring of bupivacaine in the subcutaneous space of conscious, freely-moving rats.

- Local concentrations of bupivacaine were significantly higher than systemic concentrations following SC administration of EXPAREL™ while the profiles were similar.
Project future

- Advance techniques for mobile devices that monitor drug concentration at the administration site

- Utilize mathematical models to propose corresponding bioequivalence standards

- Support bioequivalence approaches for other administration routes that could ultimately utilize local sampling (e.g. microdialysis probes)
KU...come and visit
Background

- Postsurgical pain
  - Complications
  - Poor outcomes (decreases QOL)

- Common Analgesic:
  - Opioids
    - Nausea, vomiting, respiratory depression, prolonged ileus, etc.
Local anesthetics: a component of multimodal analgesia

- Eliminate risk of catheter-related complication
- Simplicity and low cost
- Drawback
  - Short duration of analgesia.
    - 4 – 8 h for bupivacaine and ropivacaine.
DepoFoam® Technology Optimizes Pharmacokinetics and Pharmacodynamics

Drug Concentration

Free Bolus

Sustained-Release Formulation

Minimum Therapeutic Level

Time