The Structure of Bupivacaine and How it Relates to Cardiotoxicity and Lipid Rescue

By: Sean Zajdel SRNA
“The basic action of an anesthetic in the body is largely a function of the drug’s chemical structure and the resulting interaction with a cellular receptor complex.”

-John J. Nagelhout PhD, CRNA, FAAN
Disclaimer

• Conflict of Interest: None

• I have not received any compensation from anyone associated with Intralipid or any other lipid emulsion or pharmaceutical company for this presentation.
Objectives

• Describe the properties of the chemical structure of bupivacaine

• Explain the potential reasons bupivacaine is associated with increased rates of cardiotoxicity

• Describe the most current theorized mechanism of lipid rescue and how it relates to the properties of bupivacaine's chemical structure
Why is this a problem?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Amount</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td></td>
<td>$2.72</td>
</tr>
<tr>
<td>Levo-Bupivacaine</td>
<td></td>
<td>$75.00</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td></td>
<td>$164.95</td>
</tr>
</tbody>
</table>

(MIMS Medeconomics, 2017; Clint Pharmaceuticals, 2017)
Toxic Dose

• Max safe dose = **2.5 mg/kg** of bupivacaine
• 3 mcg/mL is toxic plasma concentration

<table>
<thead>
<tr>
<th>Agent</th>
<th>Duration of Action</th>
<th>Maximum Dosage Guidelines (Total Cumulative Infiltrative Injection Dose per Procedure*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine (Marcaine)</td>
<td>Long (120-240 min)</td>
<td>Without epinephrine: 2.5 mg/kg; not to exceed 175 mg total dose</td>
</tr>
<tr>
<td>Bupivacaine with epinephrine</td>
<td>Long (180-420 min)</td>
<td>With epinephrine: Not to exceed 225 mg total dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>ONSET</th>
<th>RECOMMENDED DOSE (MG/KG)</th>
<th>MAXIMUM DOSE (MG) WITH OR WITHOUT EPINEPHRINE</th>
<th>DURATION (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Fast</td>
<td>2.5</td>
<td>175</td>
<td>2-8</td>
</tr>
<tr>
<td>Peripheral block</td>
<td>Slow</td>
<td>2.5</td>
<td>175</td>
<td>4-12</td>
</tr>
<tr>
<td>Epidural</td>
<td>Moderate</td>
<td>2</td>
<td>170</td>
<td>2-5</td>
</tr>
<tr>
<td>Spinal</td>
<td>Fast</td>
<td>0.3</td>
<td>20</td>
<td>1-6</td>
</tr>
</tbody>
</table>
Bupivacaine

Lipophilic – Intermediate Amide Bond – “Hydrophilic” Tertiary Amine

(Miller, 2015; Hemmings & Egan, 2012)
Synonyms are Tough

• "Hydrophilic"

  - Lipophobic
  - Lipid insoluble
  - Polar
  - Water soluble
  - WATER LOVING

• Lipophilic

  - Hydrophobic
  - Water insoluble
  - Non-polar
  - Lipid soluble
  - FAT LOVING

Amphipathic

Like dissolves/is attracted to Like
Lipophilic substances dissolve/are attracted to other lipophilic substances
Hydrophilic substances dissolve/are attracted to other hydrophilic substances
“The more potent, lipophilic local anesthetics such as bupivacaine, tetracaine, and etidocaine are more cardiotoxic than the less lipophilic agents such as procaine, prilocaine, and lidocaine (Hemmings & Egan, 2012 p. 299).”

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>pKₐ</th>
<th>% Ionized (at pH 7.4)</th>
<th>Partition coefficient (lipid solubility)</th>
<th>% Protein binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>8.1</td>
<td>83</td>
<td>3420</td>
<td>95</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>7.9</td>
<td>76</td>
<td>366</td>
<td>64</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>8.1</td>
<td>83</td>
<td>775</td>
<td>94</td>
</tr>
</tbody>
</table>

Even the “hydrophilic” agents are almost completely ionized.

This is unlike most local anesthetics which have

No longer lipophilic NOW HYDROPHILIC
Bupivacaine

LIPOPHILIC FORM OF BUPIVACAINE

HYDROPHILIC FORM OF BUPIVACAINE

(Miller, 2015; Hemmings & Egan, 2012)
Phospholipid Bilayer
EXTRACELLULAR

INTRACELLULAR
Lipophilic hydophilicity

Activation gate

Na⁺

Selectivity filter

Inactivation gate

Resting (-90 mV)

Activated (-20 to +35 mV)

Activated (+35 to -90 mV, delayed)

(Hall, 2016; Miller, 2015; Barash, Cullen & Stoelting, 2014; Nagelhout & Plaus, 2014; Hemmings & Egan, 2012; Evers, Maze & Kharasch, 2011)
Bupivacaine Cellular Cardiotoxic Effects

(Miller, 2015; Hemmings & Egan, 2012; Bourne, Wright & Royse, 2010; Heavner, 2002)
Ca^{2+} channel
Depressant

(Hall, 2016; Hemmings & Egan, 2012; Bourne, Wright & Royse, 2010; Heavner, 2002)
Summary of Main Points Before Discussing Lipid Rescue

• Bupivacaine is the most lipophilic local anesthetic due to the long hydrocarbon chain extending from its amine group.

• “Like” dissolves/is attracted to “Like”
What is lipid rescue?

Lipid Emulsion (20%) Therapy (values in parenthesis are for 70kg patient)
- **Bolus 1.5 mL/kg** (lean body mass) intravenously over 1 minute (~100mL)
- **Continuous infusion 0.25 mL/kg/min** (~18 mL/min; adjust by roller clamp)
- Repeat bolus once or twice for persistent cardiovascular collapse
- Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low
- **Continue infusion** for at least 10 minutes after attaining circulatory stability
- Recommended upper limit: Approximately 10 mL/kg lipid emulsion over the first 30 minutes
- **REDUCE epinephrine dose to <1 mcg/kg**

(American Society of Regional Anesthesia and Pain Medicine, 2011)
Pretreatment or Resuscitation with a Lipid Infusion Shifts the Dose–Response to Bupivacaine-induced Asystole in Rats

Guy L. Weinberg, M.D.,* Timothy VadeBoncouver, M.D.,* Gopal A. Ramaraju, M.D.,† Marcelo F. Garcia-Amaro, M.D.,† Michael J. Cwik, Ph.D.‡
Figure 3. Approximately 45 Minutes After Administration of 20% Lipid Emulsion
Components of Lipid Emulsion

Micelle and Chylomicron-like Structures are Formed
“Lipid Sink”
Theorized Mechanism of Lipid Rescue

“The lipid micelle/chylomicron structure is the preferred compartment over other body areas for local anesthetic binding (Bourne, Wright & Royse, 2010)”

“Like” dissolves “like”
CACT
Theorized Mechanism of Lipid Rescue

• Carnitine-acylcarnitine transferase (CACT)
  – Mitochondrial transport protein that brings fatty acids into mitochondrial matrix to create energy
  – Bupivicaine has been found to block CACT in rats

(Bourne, Wright & Royse, 2010)
- Citrate carrier
- Carnitine/acylcarnitine translocase
- Pyruvate carrier

REDUCE epinephrine dose to <1 mcg/kg

(Giudetti et al., 2016; Bourne, Wright & Royse, 2010).
Summary
The End
Questions?

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References

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