Partition Constant and Volume of Distribution as Predictors of Clinical Efficacy of Lipid Rescue for Toxicological Emergencies
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Aim of the Study

- To look at the influence of lipophilicity of a drug for removal from serum
- To look at the influence of volume of distribution for the removal of a drug from serum by “lipid rescue”
Methods

- Drugs given to human drug free serum
- 2 mg/l concentration
- Intralipid 20 % added to; 2 % of total volume
- Mixed for 5 minutes
- Ultracentrifugation
- Serum was taken and put on columns for solid phase extraction
- Drug eluted-dried-reconstituted in 100 µl
- HPLC detection
The following drugs were tested

- Bupivacaine
- Mepivacaine
- Ropivacaine
- Amitriptyline
- Bupropion
- Haloperidol

- Lamotrigine
- Quetiapine
- Sertaline
- Verapramil
- Zolpidem
**Partition Constant Values**

- Probably the Octanol/water partition coefficient was catalogued from pubchem.
- Volume of distribution from Baselt 20004

<table>
<thead>
<tr>
<th>Drug</th>
<th>logP</th>
<th>Vd</th>
<th>Decrease of conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitryptiline</td>
<td>5</td>
<td>8 l/kg</td>
<td>52 %</td>
</tr>
<tr>
<td>Sertaline</td>
<td>4,8</td>
<td>35 l/kg</td>
<td>46 %</td>
</tr>
<tr>
<td>Verapamil</td>
<td>3,8</td>
<td>4,5 l/kg</td>
<td>34 %</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3,4</td>
<td>0,7 l/kg</td>
<td>18 %</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>3,2</td>
<td>24,0 l/kg</td>
<td>27 %</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>2,9</td>
<td>0,6 l/kg</td>
<td>7 %</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2,5</td>
<td>0,6 l/kg</td>
<td>18 %</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2,1</td>
<td>9,0 l/kg</td>
<td>13 %</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>1,9</td>
<td>1,2 l/kg</td>
<td>12 %</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1,4</td>
<td>1,1 l/kg</td>
<td>1 %</td>
</tr>
</tbody>
</table>
Results

• A good correlation between the decrease in serum concentration and the partition constant $R^2 = 0.7453$

• Still a correlation between decrease in serum concentration and Vd
  The higher the Vd the better the decrease in serum concentrations. $R^2 = 0.4645$

• I have troubles with that:
  1. Bupivacaine and Ropivacaine have a low Vd
  2. High Vd due to body- fat?
Case Reports without Local Anesthetics

- Bupropion + Lamotrigine
- Quetiapine + Sertaline
- Verapramil (sustained-release) 3X
- Diltiazem (+ Insulin)
- Nebivalol
- Diltiazem Metroprolol
- Amiodarone (+ Insulin)
- Amitriptyline
- Clomipramine (Rabbit)

- Dosulepin
- Propranolol
- Cocaine
- Dothiepin (TCA)

Abstract from the recent Congress

- Verapramil (+Insulin)
- Benzodiazepines (343)
- Quetiapine,
- Venlafaxine, Escitalopram, Bupropion, Diphenhydramine (345)
• The usual discussion is the „lipid sick“ idea the only explanation for the efficacy?
• The higher the log P (partition constant) the more likely “Lipid rescue” works
• But there are some cases with a much better partition constant and a much higher Vd were lipid rescue doesn‘t work as well as in local anesthetic poisoning
• Local anesthetics inhibit acylcarnitine translocase
• Acylcarnitine translocase is responsible for β-oxidation of long-chain fatty acids by translocation into the innermost part of mitochondria
• Perhaps so much fatty acids from “Lipid rescue” is pressed into the mitochondria restoring energy supply