Continuous Infusion Toxicity Studies in Rats; General Considerations

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Rat Infusion Model

- Jugular vein
- Femoral vein

Infusion Equipment
- Catheter
- Animal connection (tethered model)
- Infusion setup
Catheterize or not?

<table>
<thead>
<tr>
<th>Sampling method</th>
<th>Anesthetic</th>
<th>Age/sex</th>
<th>NE</th>
<th>E</th>
<th>NE+E</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decapitation</td>
<td>ND</td>
<td>20/m,f</td>
<td>—</td>
<td>—</td>
<td>46.1±4.8</td>
<td>[12]</td>
</tr>
<tr>
<td>Decapitation</td>
<td>ND</td>
<td>ND/ND</td>
<td>59.7±7.1</td>
<td>79.7±6.6</td>
<td>46.1±4.8</td>
<td>[17]</td>
</tr>
<tr>
<td>Cardiac puncture</td>
<td>Ether</td>
<td>2/ND</td>
<td>10.3±1.4</td>
<td>3.1±0.7</td>
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<td>[2]</td>
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<tr>
<td>Cardiac puncture</td>
<td>Asphyxia</td>
<td>16–32/ND</td>
<td>124.1±20</td>
<td>3.1±0.7</td>
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<td>[14]</td>
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<tr>
<td>Cardiac puncture</td>
<td>Tribromoethanol</td>
<td>ND/ND</td>
<td>21.5±2.8</td>
<td></td>
<td></td>
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<tr>
<td>Tail vein</td>
<td>ND</td>
<td>12/ND</td>
<td>13±1.4</td>
<td>0.9±0.1</td>
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<td>[11]</td>
</tr>
<tr>
<td>Retro-orbital</td>
<td>ND</td>
<td>12/m</td>
<td>17.7</td>
<td>21.8</td>
<td></td>
<td>[10]</td>
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<tr>
<td>Retro-orbital</td>
<td>ND</td>
<td>12–32/ND</td>
<td>13.5±0.7</td>
<td>13.4±0.8</td>
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<tr>
<td>Retro-orbital</td>
<td>Pentobarbital</td>
<td>9–14/ND</td>
<td>1.4±0.6</td>
<td>1.36±0.1</td>
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<td>[3]</td>
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<tr>
<td>Retro-orbital</td>
<td>Pentobarbital</td>
<td>10/m</td>
<td>6.6±1.4</td>
<td>0.5±0.1</td>
<td>4.7±0.8</td>
<td>[15]</td>
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<tr>
<td>Carotid catheter</td>
<td>ND</td>
<td>16–32/ND</td>
<td>3.8±0.6</td>
<td></td>
<td>4.7±0.8</td>
<td>[13]</td>
</tr>
<tr>
<td>Carotid catheter</td>
<td>Tribromoethanol</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td>[7]</td>
</tr>
<tr>
<td>Decapitation</td>
<td>No</td>
<td>12–18/m,f</td>
<td>24.6±2.7</td>
<td>27.3±3.8</td>
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<td>Present study</td>
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<tr>
<td>Retro-orbital</td>
<td>Halothane</td>
<td>12–18/m,f</td>
<td>5.8±0.8</td>
<td>0.4±0.1</td>
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<td>Present study</td>
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<tr>
<td>Carotid catheter</td>
<td>No</td>
<td>12–18/m,f</td>
<td>4.1±0.5</td>
<td>1.1±0.3</td>
<td></td>
<td>Present study</td>
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</tbody>
</table>

Rat Infusion Model

Which vessel to catheterize?
- Effect on pathology?
  - Surgery
  - Trauma
  - Reaction to materials
  - Site of drug entry
  - Stress (animal welfare)
- Practical aspects?
  - Animal dropouts (interruption of infusion)
  - Compound related e.g. absorption tubing
  - Efficiency e.g. daily weighing
  - TK blood sampling
Rat Infusion Model
Rat Infusion Model

Considerations for Vascular Catheterization

- Protocol; duration and frequency
- Surgical Expertise; multi disciplinary
  - Pre operated models?
  - Learning curve
- Validation of Techniques and Materials
  - Good Laboratory Practice?
  - Good Surgical Practices; aseptic technique
  - Animal Welfare; AALAC?
Infusion Equipment (1)

1) Catheter
2) Animal connection
3) Infusion setup
# Infusion Equipment (1)

<table>
<thead>
<tr>
<th></th>
<th>Silicone</th>
<th>Polyurethane</th>
<th>Polyethylene</th>
<th>PVC</th>
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<tbody>
<tr>
<td>Biocompatibility</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Fair</td>
<td>Fair</td>
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<tr>
<td>Compound compatibility</td>
<td>Possible reacting</td>
<td>Possible reacting</td>
<td>Inert</td>
<td>Possible reacting</td>
</tr>
<tr>
<td>Stiffness</td>
<td>Soft</td>
<td>Soft</td>
<td>Stiff</td>
<td>Soft or stiff</td>
</tr>
<tr>
<td>Ease of insertion</td>
<td>Difficult</td>
<td>Moderately easy</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Sizes available</td>
<td>Many</td>
<td>Many</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Ease of bonding</td>
<td>Excellent</td>
<td>Fair</td>
<td>Poor</td>
<td>Fair</td>
</tr>
<tr>
<td>Memory</td>
<td>Excellent</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Tear strength</td>
<td>Poor</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Sterilization</td>
<td>EtO, steam</td>
<td>EtO</td>
<td>EtO, steam</td>
<td>EtO, limited steam</td>
</tr>
</tbody>
</table>

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Design
- Tip Geometry
- Material
- Size
- Implantation length
- Biocompatibility (Heparin Coating, CBAS)
Mean Catheter Patency Duration by Tip Configuration

- Rounded Tip: Mean Patency Duration (days) = 27.83, n = 30
- Blunt Tip: Mean Patency Duration (days) = 19.90, n = 30

* p < 0.0001

Error Bar Confidence Limits: 95%
Infusion Equipment (2)

Animal Connection Device
- **Covance Harness**
- **Dacron Button**
- Subcutaneous Access Port
- Tail Cuff
- Dental Cement; head attachment
Infusion Equipment (2)
Considerations for Vascular Catheterization

- Connection method
  - Efficient; e.g. weighing
  - Aseptic

- Tethering setup
  - Sterile kits; disposable

- Tubing
  - Medical grade

- Caging
  - Dedicated?
Thank You

Questions?