Implantable infusion pumps for chronic rodent studies

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Scientific Application

• Chronic administration of pharmacological agents to non-tethered rodents.

• Routes of administration:
  – Subcutaneous
  – Intraperitoneal
  – Intravenous
  – Intracerebroventricular

• Duration of studies: days to weeks
Current available options

• **Alzet** osmotic minipumps ([www.Alzet.com](http://www.Alzet.com))
  – Rats and mice
  – Relatively inexpensive
  – Variable reproducibility

• **iPrecio** ([www.iPrecio.com](http://www.iPrecio.com))
  – Rats and larger species
  – Relatively expensive
  – Programmable and refillable in vivo
  – Precise and reproducible
Outline

• Alzet pumps
  – Pump design and models available
  – Filling and implanting pumps

• iPrecio pumps
  – Pump design
  – Filling and programming the pump
  – Implanting pumps

• Cost comparison

• Real world experiences with both pumps

• Summary: Pros and cons
Alzet: Design and models

Design Concept

Osmotic movement of body fluids into the “osmotic layer” compresses internal reservoir which displaces infusate into the catheter.

Fixed Infusion Rates: 0.11 to 10 μl/hr
Durations: 1 day to 6 weeks

- 100 μl
- 200 μl
- 2 mL
Alzet applications

• Implantation site
  – Subcutaneous
  – Intraperitoneal
• Routes of administration
  – Subcutaneous
  – Intraperitoneal
  – Intravenous
  – Intracerebroventricular
  – Fat pads
Alzet: Filling the pump

ALWAYS USE GLOVES! The natural oils from your hands will damage the exterior of the pump casings.

Weigh the empty pump (body + flow regulator) and record weight.

Use needle supplied with pumps to draw infusate into syringe.

Be sure all air bubbles are removed from the syringe.

USE CARE when inserting filling needle/syringe into pump body so you don’t puncture the bladder.

Fill the pump slowly and retract needle as it fills.

Stop filling when a bead of infusate rises out of the pump.
Alzet: Filling the pump

Withdraw needle and insert flow regulator into pump.

Reweigh the pump and record. Increase in weight should equal the filling volume.

Keep pump upright until it is implanted.

You may or may not choose to prime the pump before implantation.
Alzet: Implanting the pump

Use sterile technique!

Subcutaneous implantation

Intraperitoneal implantation
iPRECIO

Design Concept
Roller peristaltic pump that transfers infusate from reservoir to the catheter.
6 month battery life (@ 0.1 ul/hr flow rate).

Port for refilling
900 ul reservoir
Roller pins
Catheter
iPRECIO is programmable

**Infusion modes:** Instant or post recovery (delayed)

**Flow rate modes:** Constant or variable from 1 to 30 ul/hr in 0.1 ul/hr steps (up to 10 different rates)
iPRECIO
Refillable design

• Refill by insertion of needle through the skin.

• Long duration of infusion periods.

• Ability to change infusates at any time during the protocol (e.g., "washout period").
What does it cost?

Alzet

Model 1002: $28/pump
Model 2004: $28/pump
Model 2ML2: $33/pump

iPRECIO

1) Software/management system-$1700.00
2) Pump cost = $1250.00/5 pumps
   = $250/pump

Note: sold as a “single use” pump but it is possible to resterilize and reuse.
Real world experiences with both Alzet and iPRECIO implantable pumps
Osborn, Kuroki and Fink

Current Hypertension Reports, 2011
AngII-salt hypertension in the rat

Most measurements made continuously over entire experimental protocol
- Arterial pressure and heart rate (telemetry)
- Sympathetic nerve activity (hardwired and telemetry)
- Whole body and regional norepinephrine spillover

High NaCl diet: 2.0%
Normal NaCl diet: 0.4%
Low NaCl diet: 0.1%
The “classic” AngII-salt response

Recent unresolved issue with Alzet pumps:
Failure to maintain the hypertension

Questions
Poor reproducibility in pump rates?
Degradation of AngII in the pump?
Why is this a new problem?

Same protocol and dose of AngII
Variable infusion rates do not explain the variable pressure responses

Theoretically the 2ML2 model:

- pumps at 5 μL/hr which is...
- 0.12 mL/24h which is...
- 1.68 mL over 14 days
- Residual volume = 0.32 mL

The rate is slower than predicted and quite variable
Many proteins adsorb nonspecifically to plastic materials. ALZET pumps are manufactured from elastomers selected to minimize adsorption. However, if adsorption is a concern, DURECT recommends addition of 1-5% protease-free serum albumin to the vehicle for infusion.
Addition of BSA to infusate improves the “slow pressor AngII model” in the mouse (Davisson Lab, Cornell)
Addition of BSA to infusate has no effect in the “AngII-salt model” in the rat (Osborn Lab)
Big pumps and small pumps are not the same
Comparison of iPRECIO and Alzet

MAP (mmHg)

Insert Alzet and iPrecio pumps

Filled iPrecio pumps with Saline

Removed Alzet Pumps

Hours

Alzet n=3
iPrecio n=3

Filled iPrecio pumps with Saline

Removed Alzet Pumps
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<td>Mice and rats</td>
<td>Variability</td>
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<tr>
<td>Programmable</td>
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<td>High precision</td>
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<td>Up to 6 month infusions</td>
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