iPRECIO Programmable Pumps: Enabling Drug Delivery Technology

Tsung Tan
May 1, 2014
Manufacturer of ALZET Osmotic Pumps

Authorized distributor of iPRECIO Programmable Pumps in North America
Presentation Outline

• A brief history of iPRECIO® Infusion Pumps
• Drug Delivery – implantable pumps
• iPRECIO pumps for mice (SMP-300) and rats (SMP-200) - Key specifications
• Routes of Administration
• Research applications: Refillable and programmable features in cardiovascular, cancer, behavior,
• Future applications
• Questions and Answers
Primetech Corporation

Manufacturer and distributor of high technology medical and analytical science products

- Establishment: April 2\textsuperscript{nd} 1988
- Sister Company: Primetech Engineering Corp.
- Head Office: Tokyo, Branch in Osaka
- Number of employees: 50

- Mission: Create true value…
Our Mission
Create true Value for our Life science Customers

iPRECIO® Infusion Pumps
- Make it as easy as possible to evaluate efficacy/toxicity of molecules/agents in different animal models and species. (ambulatory in-vivo or jacketed)
- Make the results as relevant as possible to the clinic.
(Exposure profile, quantitative pharmacology, untethered free moving (stress free, group housing (socialization), ....)

The use of iPRECIO® pumps will have a positive impact on experimental conditions and the relevance of results achieved. Initial costs may be higher but in the long run the use of the pump could be cost saving in the context of the whole compound development.

The ambulatory model (in-vivo or jacketed) reduces stress and provides cleaner results. Greater sensitivity!!!

www.iprecio.com
Implantable pumps for drug delivery

- Successful use of implantable pumps found in nearly 15,000 scientific publications.
- Their versatility in delivery continuous infusion, intermitted or complex infusion protocols acutely or chronically has made them ubiquitous in drug discovery and basis research.
- Implantable pumps are a very convenient and cost effective method to deliver drugs for biochemical research in the pharmaceutical industry.
- Important research tool for investigating continuous infusion versus the typical peak to trough exposure profiles of bolus injections etc.
- Significant animal welfare benefits over repeat dosing.

Related Publications
Culwell, J.A., Gadea, J.R., Peer, C.E., Wright J.C.
Implantable Drug Delivery Systems Based on the Principles of Osmosis
Advances in Delivery Science and Technology, Springer 2012
http://dx.doi.org/10.1007/978-1-4614-0554-2_17

Tan T., Watts S. W. and Davis R. P.
Drug delivery: enabling technology for drug discovery and development. iPRECIO Micro Infusion Pump: programmable, refillable, and implantable.
Key Components of an iPRECIO® Micro Infusion Pump

- An accurate & reliable pump mechanism: patented “Rotary Finger” Mechanism
  - Pulse micro-motor and gear mechanism
  - CAM and projections to manipulate the “Rotary Finger” mechanisms

- Microprocessor (CPU) and associated circuitry (memory, input/output, ……) for controlling the pump mechanism

- A method for programming and communicating with the pump.
  - Application Software on PC for programming and managing pumps
  - Infrared (IR) or Wireless technology including antenna

- At least one power source
  - Battery

- Protection against water/humidity ingress and contamination of Test Article (TA) or Maintenance (MA) – vehicle/solvent and biocompatible with life/body.

- Fluidics
  - Reservoir for TA or MA (as chemically resistant as possible)
  - Catheter
  - Filling /refilling port
An accurate and reliable Rotary Finger pump mechanism

Internally, a micro-motor slowly revolves in a clockwise direction turning the cam with its four projections. In each quarter rotation, a single cam projection sequentially pushes up each of the seven finger pins.

This continuous cycle compresses the liquid filled tube, creating a peristaltic like movement of the fluid.

As the solution moves through the tube from right to left, it is forced from the reservoir of the pump into the test subject.

The accuracy of the pump is +/- 5%.
**NEW**

**SMP-300**

- **24.8mm**
- **15.0mm**
- **H: 7.2mm**
- **Weight: 3.3g**

**SMP-200**

- **38.7mm**
- **19.2mm**
- **H: 9.7mm**
- **Weight: 7.9g**

Antenna
The antenna length is 50mm.
- 0.1mm OD titanium wire is inserted into 0.4mm OD PU tubing. (1.2Fr or 0.017" OD)
iPRECIO® Micro Infusion Pumps have 3 key features

- **Implantable**
  - Totally implanted in the subcutaneous space

- **Refillable**
  - Refillable percutaneously through the septum in the pump’s reservoir

- **Programmable**
  - Programmable Infusion protocol up to 10 different flow steps
Implantable

- The pump can be completely implanted in small laboratory animals subcutaneously. Thus, the animal moves freely without any restrain (i.e. tethering) during drug infusion. Additionally, infection risk is reduced, and the animal likely is less stressed than it would be in a tethered infusion model.
• You can replenish the pump with any medical fluid via the percutaneous access to the pump through the refill septum and reservoir after implantation. So, long-term drug infusion can continue until the installed battery life has run out. The reservoir is elastic and configured in such a geometry as to allow gentle palpation to confirm an approximate level of fluid in the reservoir.
Refilling Reservoir
The top view of the pump

- Suture Anchor
- Refilling Septum
- Patented “Rotary Finger” Mechanism
- Finger pin
- Cam
- Micro-motor
- Outlet
- 900μl Reservoir
- Suture Anchor
The bottom view of the pump

- IR for Transmission
- CPU Circuit
- Suture Anchor
- Battery
- IR for Receiving
The antenna length is 50mm.

- 0.1mm OD titanium wire is inserted into 0.4mm OD PU tubing. (1.2Fr or 0.017" OD)
# Comparison of Key Specifications

<table>
<thead>
<tr>
<th>Model</th>
<th>IMS/SMP-300</th>
<th>IMS/SMP-200</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance of the pump</strong></td>
<td><img src="image1.png" alt="Image of pump" /></td>
<td><img src="image2.png" alt="Image of pump" /></td>
</tr>
<tr>
<td><strong>Used Same Rotary Finger Method (Patented Peristalsis) in both models.</strong></td>
<td><img src="image1.png" alt="Image of pump" /></td>
<td><img src="image2.png" alt="Image of pump" /></td>
</tr>
<tr>
<td><strong>Size [L] x [W] x [H]</strong></td>
<td>24.8x15.0 x 7.2 mm &lt;3.3g / 2.15cc&gt;</td>
<td>38.7 x 19.2 x 9.7mm &lt;7.9g / 7.20cc&gt;</td>
</tr>
<tr>
<td><strong>Animal Species</strong></td>
<td>Mouse or larger</td>
<td>Rats or larger</td>
</tr>
<tr>
<td><strong>Animal Size</strong></td>
<td>Recommend : 25g / Min. : 20 g</td>
<td>Recommend : 230 g / Min. : 160 g</td>
</tr>
<tr>
<td><strong>Outlet Catheter (Material, Size, Length)</strong></td>
<td>Medical Grade SEBS , 100mm 3.6Fr (ID 0.55mm/0.0216in)</td>
<td>Medical Grade SEBS , 135mm 3.6Fr (ID 0.55mm/0.0216in)</td>
</tr>
<tr>
<td><strong>Reservoir Volume</strong></td>
<td>130 μL</td>
<td>900 μL</td>
</tr>
<tr>
<td><strong>Flow Rate (Setting Resolution)</strong></td>
<td>0.1 – 10.0 μL/hr (0.1μL/hr)</td>
<td>0, 0.2, 0.5 &amp; 1.0 – 30.0 μL/hr (0.1μL/hr)</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>+/- 5% (under 0-80cmH₂O pressure condition)</td>
<td>+/- 5% (under 0-80cmH₂O pressure condition)</td>
</tr>
<tr>
<td><strong>Package / Type of Usage</strong></td>
<td>EO Sterilized Blister individual package, Disposable</td>
<td>EO Sterilized Blister individual package, Disposable</td>
</tr>
</tbody>
</table>

Used Same Rotary Finger Method (Patented Peristalsis) in both models.
## Comparison of Key Specifications

<table>
<thead>
<tr>
<th>Model</th>
<th>IMS/SMP-300</th>
<th>IMS/SMP-200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of the data communication device</td>
<td><img src="image" alt="UCD-300 Image" /> 120(L) x 77(W) x 31(H)mm / 167g</td>
<td><img src="image" alt="UCD-200 Image" /> 120(L) x 67(W) x 35(H)mm / 147g</td>
</tr>
<tr>
<td>Data Communication Method</td>
<td><strong>Wireless</strong>&lt;br&gt;Japan, North America: 915MHz - 928MHz&lt;br&gt;Europe: 863MHz - 870MHz</td>
<td><strong>IR Communication</strong></td>
</tr>
<tr>
<td>Software Programming Capability</td>
<td><strong>Anytime user can make and save infusion protocols</strong> and could be load them to the pumps/animals. More simple and easy to learn.&lt;br&gt;• Up to 16 flow steps programmable&lt;br&gt;• Repeat Mode</td>
<td><strong>Have infusion mode selection and Flow Rate Mode selection</strong>&lt;br&gt;• 10 flow-steps&lt;br&gt;• Repeat mode</td>
</tr>
<tr>
<td>PC Compatibility of software, Connection w/ Data communication device</td>
<td><strong>Win XP and 7 (32bit and 64bit)</strong> via <strong>Ethernet Cable</strong> (Cross type)</td>
<td><strong>Win XP and 7 (32bit + 64bit)</strong> via <strong>USB Cable</strong></td>
</tr>
<tr>
<td>Management system and software</td>
<td>Software should be purchased at fist time only per laboratory (customer). Customer can purchase UCD-300 separately from the software. (i.e. can be copied on multiple PCs)</td>
<td>Software and Data Communication device are bundled and should be purchased together.</td>
</tr>
</tbody>
</table>
# Comparison of Battery Life

**SMP-300**

<table>
<thead>
<tr>
<th>Flow Rate</th>
<th>Continuous Infusion</th>
<th>Total Infusion Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(days, approx.)</td>
<td>(hours)</td>
</tr>
<tr>
<td>0.1 μL/hr</td>
<td>18 days</td>
<td>444.3 hr</td>
</tr>
<tr>
<td>1.0 μL/hr</td>
<td>16 days</td>
<td>387.1 hr</td>
</tr>
<tr>
<td>5.0 μL/hr</td>
<td>10 days</td>
<td>246.3 hr</td>
</tr>
<tr>
<td>10.0 μL/hr</td>
<td>7 days (1 week)</td>
<td>169.3 hr</td>
</tr>
</tbody>
</table>

**SMP-200**

<table>
<thead>
<tr>
<th>Flow Rate</th>
<th>Continuous Infusion</th>
<th>Total Infusion Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(days, approx.)</td>
<td>(hours)</td>
</tr>
<tr>
<td>1.0 μL/hr</td>
<td>6 months</td>
<td>4,328 hr</td>
</tr>
<tr>
<td>8.5 μL/hr</td>
<td>1 month</td>
<td>669 hr</td>
</tr>
<tr>
<td>19.0 μL/hr</td>
<td>1.8 weeks</td>
<td>307 hr</td>
</tr>
<tr>
<td>30.0 μL/hr</td>
<td>1 week</td>
<td>196 hr</td>
</tr>
</tbody>
</table>
Programmable

• You can set your own infusion protocol (Start/Stop day/time, Flow rate etc.)

→ Download your protocol to the pump via communication device.
iPRECIO® Management System: IMS-200

Variable Infusion with repeat Mode

<table>
<thead>
<tr>
<th>Step</th>
<th>Duration</th>
<th>Flow Rate (ul/hr)</th>
<th>Date/Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>2</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>3</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>4</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>5</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>6</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>7</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>8</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>9</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
<tr>
<td>10</td>
<td>00</td>
<td>20</td>
<td>09/17/02 18:00</td>
</tr>
</tbody>
</table>

Flow pattern / Times (Hr(s))

Program1 Times(3)

Program1 Times(2)

Program1 Times(10)
iPRECIO® Management System: IMS-300
Routes of administration

Influenced by

- Intended route of administration in clinical
- Regulatory requirements
- Systemic or site directed administration
- Formulations, flow-rates, ..........

Related Publications


Administration of Substances to Laboratory Animals: Equipment Considerations, Vehicle Selection, and Solute Preparation
Patricia V Turner, Cynthia Pekow, Mary Ann Vasbinder, and Thea Brabb

Administration of Substances to Laboratory Animals: Routes of Administration and Factors to Consider
Patricia V Turner, Thea Brabb, Cynthia Pekow, and Mary Ann Vasbinder
Selected Technical Notes and FAQ

*Intracerebroventricular infusion with Brain infusion cannula (Plastic One)*
Selected Technical Notes and FAQ

Intrathecal infusion with custom 32G Recathco Catheter

Fig. 2 Intrathecal Catheter Preparation
Research Applications

Cancer, Cardiovascular and Behaviour
iPRECIO® Applications - Cancer

- Starting to be viewed upon as a heterogeneous disease
- The efficacy of combination treatments for cancer depends on drug order and timing
- Narrow therapeutic index
- Chronopharmacology infusions to improve patient outcomes
- Sequential application of anticancer drugs
- Combination application of anticancer drugs

- Immunosuppressed animal models (secondary infections/complications)
- One surgery of cancer cell implantation and pump
  - Initially infusing saline during recovery and tumor growth
  - Agent infusion on confirmation of tumor size based on luminescence/etc.

CAMBRIDGE, Mass.—Combination therapies have become one of the new standards in cancer care, due to their increased efficacy over singular drugs, but a recent study by researchers at the Massachusetts Institute of Technology (MIT) has revealed that the timing of combination therapies might bolster their effectiveness even further. The team discovered that staggering the administration of two cancer drugs significantly increased their ability to destroy breast cancer cells.
We could identify several putative advantages when compared to existing infusion methods:

- only one surgery is required for both, the tumor cell injection and the pump implantation causing less distress to the animals
- the infusion protocol can include a recovery period phase where only saline is infused to keep the catheter patent. Then at an operator defined time (related to tumor size), infusion of the therapeutic can be started
- there will be much less limitations in relation to the solubility of the substance, the prepared concentration of the substance, and the limited range of infusion rates with this pump
iPRECIO® Functionality: Extraction/refilling

Cranial / Brain Infusion

- In particular, this evaluation system to monitor the activity changing from baseline in an i.c.v. infusion can realize only iPRECIO that there is not the influence on activity by anesthesia and handling.
- only one surgery is required for both, the tumor cell injection and the pump implantation causing less distress to the animals
- the infusion protocol can include a recovery period phase where only saline is infused to keep the catheter patent. Then at an operator defined time (related to tumor size), infusion of the therapeutic can be started
- there will be much less limitations in relation to the solubility of the substance, the prepared concentration of the substance, and the limited range of infusion rates with this pump

Related Publications

Schnell C. and Ferrat T.,
Use of novel programmable pump for intracranial administration in an orthotopic glioblastoma tumor model in rats.
DSI User Group Meeting, Paris, France; March 17th 18th 2011

Copeman C, Perron J., Trudel Y., Caron S., Emond F., Frenette, and Burr M.
Intraventricular Infusion in the albino rat
Society of Toxicology Annual Meeting, San Francisco, United States, March 11th to 14th 2012.

Yamato M., Okuyama K., Jin GH., Eguchi A., Watanabe Y., Kataoka Y.
Endogenous IL-1β and IL-1 receptor antagonist in the brain are involved in poly I:C-induced immunological fatigue
The 33rd Annual Meeting of the Japan Neuroscience Society, Kobe, Japan., September 2nd – 4th 2010.

Yamato M., Okuyama K., Jin GH., Eguchi A., Watanabe Y., Kataoka Y.
Interleukin-1 β expression in the brain is involved in poly I:C-induced immunological fatigue-like behavior in rats
The 32nd Annual Meeting of the Japan Neuroscience Society, Nagoya, Japan., September 16th - 18th 2009.

Gonadotropin-Inhibitory Hormone Is a Hypothalamic Peptide That Provides a Molecular Switch between Reproduction and Feeding.
iPRECIO® Applications - Cardiovascular

• Radiotelemetry (telemetry) has become the gold standard for monitoring physiological data in unrestrained, conscious laboratory animals.
• The physiological parameters measured through telemetry include mean arterial blood pressure, heart rate activity and temperature, to name a few.
• The use of stress-free laboratory animals leads to higher sensitivity for drug induced effects and lower variability of parameters measured.
• In combination with his gold standard, sophisticated implantable pumps will lead to ever more sensitive and powerful means of detecting drug induced therapeutic and/or adverse effects.

Related Publications
Tontodonati M., Fasdelli N., Moscardo E., Giarola A., and Dorigatti R.
A canine model used to simultaneously assess potential neurobehavioural and cardiovascular effects of candidate drugs.

Baseline values compared

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate</th>
<th>BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESTRAINED</td>
<td>~400 bpm</td>
<td>~140 mmHg</td>
</tr>
<tr>
<td>TETHERED</td>
<td>~380 bpm</td>
<td>~120 mmHg</td>
</tr>
<tr>
<td>TELEMETRY</td>
<td>~310 bpm</td>
<td>~100 mmHg</td>
</tr>
</tbody>
</table>

*Courtesy of UCB Pharma, Belgium / DSI telemetry for heart rate and BP*
Distribution of mean blood pressure (MBP) & heart rate (HR) in normotensive restrained (==; n=55) or freely moving (—; n=67) marmosets

Lower baseline BP & HR > less intra & inter-animal variation > enhanced statistical power

> REDUCTION IN ANIMAL USE (DSI telemetry for blood pressure and heart rate)
iPRECIO®: Ctrl, start/stop and dose response

Davis et al. (Davis et al., 2010) previously established, using both the iPRECIO® micro infusion pump and radiotelemetry devices, that 5-HT administration produced repeated falls in blood pressure in the sham (normotensive) and deoxycorticosterone acetate (DOCA)-salt (hypertensive) rat when the pump was turned on. When the pump was turned off (0.2µl/hour), blood pressure returned to normal. This study demonstrated that an equivalent effect was possible at a much lower dose than was previously studied (25 µg/serotonin hydrochloride /kg/min) in the sham and DOCA-salt rat.

Related Publications
Tan T., Watts S. W. and Davis R. P.
Drug delivery: enabling technology for drug discovery and development. iPRECIO Micro Infusion Pump: programmable, refillable, and implantable.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3149148/

Jay Gizzi, Theodore Baird, Kyle O'Donohue, Josh Yoder, Jessica Grenwis, and Heather Bogie
Optimization of a fully implantable small animal infusion model involving multi-pressure data collection.
FASEB J. 2010 24:lb571 www.fasebj.org/cgi/content/meeting_abstract/24/1_MeetingAbstracts/lb571

Diaz J., Ni W., Thompson J., King A., Fink G.D., and Watts S.W.
5-Hydroxytryptamine Lowers Blood Pressure in Normotensive and Hypertensive Rats
JPET 325:1031–1038, 2008

Watts S.W., Morrison S.F., Davis, R.P., and Barman S.M.
Serotonin and Blood Pressure Regulation
http://pharmrev.aspetjournals.org/content/64/2/359.abstract
LV contractility was increased by successive doses of dobutamine; arterial systolic pressure was unaffected.

LV contractility and arterial systolic pressure were similarly decreased by administration of successive doses of verapamil.

Related Publications
Tan T., Watts S. W. and Davis R. P.
Drug delivery: enabling technology for drug discovery and development. iPRECIO Micro Infusion Pump: programmable, refillable, and implantable.

Jay Gizzi, Theodore Baird, Kyle O'Donohue, Josh Yoder, Jessica Grenwis, and Heather Bogie
Optimization of a fully implantable small animal infusion model involving multi-pressure data collection.
FASEB J. 2010 24:lb571 http://www.fasebj.org/cgi/content/meeting_abstract/24/1_MeetingAbstracts/lgpl71
iPRECIO® : Recovery, Exchange & Refilling

Behaviour
Yamato et al used iPRECIO® as an enabling technology to allow baseline activity to be monitored after implantation of pump with brain infusion cannula in place while it only infused vehicle/solvent. (Yamato et al., 2010) The effect of agent/drug on animal activity compared to its baseline could then be analyzed without the effect of handling and anesthesia.

The infusion pumps enhanced the delivery of the drug and allowed for us to identify a clean behavioral antidepressant effect, devoid of complications due to daily injections or tissue irritation as occurs with osmotic pumps.

Related Publications
Yamato M., Okuyama K., Jin GH., Eguchi A., Watanabe Y., Kataoka Y.
Endogenous IL-1β and IL-1 receptor antagonist in the brain are involved in poly I:C-induced immunological fatigue
The 33rd Annual Meeting of the Japan Neuroscience Society, Kobe, Japan., September 2nd – 4th 2010.

Yamato M., Okuyama K., Jin GH., Eguchi A., Watanabe Y., Kataoka Y.
Interleukin-1 β expression in the brain is involved in poly I:C-induced immunological fatigue-like behavior in rats
The 32nd Annual Meeting of the Japan Neuroscience Society, Nagoya, Japan., September 16th - 18th 2009.

Wood S.K., McFadden D.V., Grigoriadis D., Bhatnagar S. and Valentino R.J.
Depressive and cardiovascular disease co-morbidity in a rat model of social stress: a putative role for corticotropin-releasing factor
Research Applications

Additional Examples
iPRECIO SMP-200

Not only for Rat. - Rabbit, Dog, NHP, Cell culture

Enhanced resistance to permeability transition in interfibrillar cardiac mitochondria in dogs: effects of aging and long-term aldosterone infusion

CALL FOR PAPERS
Mitochondria in Cardiovascular Physiology and Disease

Enhanced resistance to permeability transition in interfibrillar cardiac mitochondria in dogs: effects of aging and long-term aldosterone infusion

A miniaturized microfluidic cell culture system driven by a miniaturized infusion pump

A miniaturized microfluidic cell culture system is presented. The system consists of a microfluidic device and a miniaturized infusion pump that possesses a reservoir of culture medium, an electrical control circuit, and an internal battery. The footprint of the system was downsized to 87 x 57 mm, which is, to the best of our knowledge, the smallest cell culture device with a built-in miniaturized infusion pump. The system was compact and easy to use.
# iPRECIO® SMP-200®: with Mouse

<table>
<thead>
<tr>
<th>Customer</th>
<th>Animal</th>
<th>Drug</th>
<th>Administration Route</th>
<th>Mode</th>
<th>Flow-rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiroshima Univ.</td>
<td>Mice</td>
<td>Bretazenil</td>
<td>Brain</td>
<td>RCV/Constant</td>
<td>2ul/hr</td>
</tr>
<tr>
<td>Hokkaido Univ.</td>
<td>Mice</td>
<td>Confidential</td>
<td>External jugular vein</td>
<td>RCV/Variable</td>
<td>0.1-30ul/hr</td>
</tr>
<tr>
<td>National center of Neurology and Psychiatry</td>
<td>Mice</td>
<td>Sialic acid synthase</td>
<td>subcutaneous</td>
<td>Instant/Constant</td>
<td>10ul/hr, 3ul/hr</td>
</tr>
<tr>
<td>Jichi medical univ.</td>
<td>Mice</td>
<td>Diabetes related medicine</td>
<td>External jugular vein</td>
<td>RCV/Constant</td>
<td>3ul/hr, 10ul/hr</td>
</tr>
</tbody>
</table>
iPRECIO® : Agent dosing times

Matsuoka et al. used iPRECIO® pumps to administer vitamin B12 at onset of the light cycle and at the onset of the dark cycle to study the effect B12 on the arousal and body temperature rhythm (Matsuoka et al., 2007).

Zaretsky et al. used iPRECIO® pumps to inject 100nl of bicuculline solution four times over 2 days. Telemetry recordings showed 4 distinct injections. Injections number 3 and 4 were obviously like injections 1 and 2 but blurred by the animal’s intrinsic activity before and during darkness.

Related Publications
Emiko Matsuoka, Makoto Miyazaki, Kazunori Iwanaga, and Masao Kakemi.

Assessment of Pharmacokinetic-Pharmacodynamic Relationship of Vitamin B12 in the Treatment of Somnipathy in Rats
14th Annual Meeting of Japanese Society for Chronobiology, Tokyo, Japan, November 7-9 2007

Zaretsky D.V., Zaretskaia M.V., Durant P.J., Rusyniak D.E.
The use of microinfusion pump to perform intrahypothalamic injections in conscious rats.
Neuroscience 2012, New Orleans, USA., October 13 th - 17 2012

Zaretsky DV, Zaretskaia MV, Rusyniak DE, Dimicco JA.
Stress-free microinjections in conscious rats
iPRECIO® : Bolus Applications

15 µl volume bolus at 5, 10, 20 & 30 µl/hour with 0 µl/hour to complete 24 hour cycle, repeated daily

- 60 day evaluation: One 15µl bolus injection per 24 hour
- Test Agent (TA) = water: Total Volume Error = -1.2% to -3.0%

% deviation from programmed volume vs Days since start of bolus protocol

5µl/h for 3 hours (Tot. Vol Error -1.5% 60 days)
10µl/h for 1.5 hours (Tot. Vol Error -1.4% 60 days)
20µl/h for 0.75 hours (Tot. Vol Error -1.2% 60 days)
×30µl/h for 0.5 hours (Tot. Vol Error -3.0% 60 days)
Intrathecal Infusion

- The ability to refill the pump every 2 to 3 days allowed proteins to be replaced due to stability.
- 1 month study duration but require to refill weekly due to stability of test agent.
- iPRECIO good for formulations (proteins, peptides, biologics, …… ) which have short stability in-vivo.
- Analgesic tolerance comparisons for constant dosage against versus intermittent.
  - Bolus of 5µl several times per day versus continuous infusion
  - PK study to confirm exposure levels

Related Publications

Patar, A., Jaafar, H., Jamalullai, S. M. S. S., & Abdullah, J. M.
The body wall crude extract of Stichopus variegatus promotes repair of acute contused spinal cord injury in rats by improving motor function and reduces intramedullary hemorrhage.

Yoshinori T., Kenji S., Kazuharu S., and Gozoh T.
Extracellular phosphorylation is a novel target for regenerative medicine against spinal cord injury. The FASEB Journal. 2012;26:921.4,
http://www.fasebj.org/cgi/content/meeting_abstract/26/1_MeetingAbstracts/921.4?sid=8d804f68-eb3f-4c2c-8b12-fa525cbbb359

Yoshinori T.,
Extracellular protein phosphorylation promotes functional recovery from experimental spinal cord injury.
The 6th International Symposium on Receptor Mechanisms, Signal Transduction and Drug Effects - Development of Novel Therapy to Specific Disease in organ -, Kyoto, Japan; April 1st and 2nd 2011

Imai T., Nakata E., Inoue K.
Inhibition of P2X4 receptor on spinal microglia attenuates mechanical allodynia in experimental autoimmune neuritis rats
Pain Research, Vol. 26 2011, O-59
iPRECIO® : Extracting/Refilling every 3 days

Buehler et al. used iPRECIO® to infuse Cell-free hemoglobin (Hb) to the left jugular vein. Pumps were refilled with fresh aliquots of Hb every 3 days. Prior to refilling, residual Hb in the pumps reservoir was removed and the oxidative states of residual Hb were determined by UV-visible spectrophotometry. Spectral analysis of pump residual Hb demonstrated insignificant intrapump autoxidation prior to refill compared with Hb starting material. Pump residual Hb composition over the course of the study was 84.3 ± 6.0% ferrous, 11.2 ± 7.3% ferric, and 6.6 ± 6.2% hemichrome. Study duration of up to 7 weeks.

Anesthesia : Isoflurane
Site preparation: Shaving the animal skin area each time we injected thoroughly scrubbing the injection site with antimycrobial solution
We did not have any issues with anesthesia during pump implants, rats recovered quickly and we had no mortality rate
Never reusing needles.clean for each animal

Related Publications
Free hemoglobin induction of pulmonary vascular disease: evidence for an inflammatory mechanism.
PK data with iPRECIO® and Valsartan®

Valsartan® Exposure

ng/mL vs. in hours post dose

- 30ul/hr 24hrs
- 3ul/hr 24hrs
- 10ul/hr 24hrs
Validation and use of the iPrecio® micro-infusion pump on GLP studies

J. Perrot, V. Frenette, C. Copesper
Charles River Laboratories Preclinical Services Montreal Inc., 22622 Transcanadienne, Sennville, Quebec, Canada H9X 3R3

Introduction

Low infusion rates are generally required for conduct of preclinical studies using non-standard routes of administration such as intracerebral, intrathoracic or subcutaneous injection or possibly other target tissue dosing. Achieving these low rates of infusion with standard infusion pumps also presents several challenges. Various types of min or micro-infusion pumps can be used, but have several drawbacks including providing reproducible and accurate delivery which is important for the conduct of regulatory compliant studies. Our laboratory selected an implantable programmable micro-infusion pump, the iPrecio® micro infusion pump, and evaluated its accuracy of delivery for possible use in regulatory compliant studies requiring very low infusion rates.

Material and Methods

Micro-infusion pump

The iPrecio® micro infusion pump is indicated to allow infusate rates of 1 to 50 μL/hr, with up to 4 combination of settings. This allows flexibility in the programming, permitting the use of different rates for each, or alternate solution post-surgery, and the programming of dosing cycles and/or without periods between formulations tested for combination schemes.

Implantation

The iPrecio® micro infusion pump is supplied with an outlet-solution catheter, which may be coupled with different types of catheters depending on the route of administration. The pump is surgically implanted subcutaneously, and anchored to the musculature with non-absorbable suture material. The refillable pump reservoir is accessible via a port, which is easily located under the skin by palpation. The refill procedure necessitated minimal restraint, resulting in minimal stress to the animal.

Method of infusion

The pump is controlled with software that automatically triggers the pump to deliver the programmed volume of solution. This is achieved by selecting the desired volume in the starting point, the desired flow rate in the ending point, and the total duration of infusion.

Results and Conclusion

Our validation study demonstrated the successful implantation of iPrecio® pumps with little or no complications, the ability to use the pumps in a number of dosing schemes, and that the software accurately programmed the infusion pumps to deliver 1 or 50 μL/hr for 24-48 hours, with minimal necessary programming changes. The mean accuracy of delivery was 100% ± 5%.

References

iPrecio® User Manual ver. 3.0.0 e
www.iprecio.com
iPRECIO® : Future Applications

Programmable implantable infusion pumps in the metabolic field to optimize the drug delivery pattern. Manuscript submitted for publication.

Example Recent Use
We use them for studies to understand the PK-PD relationship of specific molecules. In terms of the infusion protocol it would be multiple steps to achieve a specific PK concentration in a PD study.

Lead optimization phase
Understanding PK-PD in animal models in detail for translation as aspects and to understand PK-PD in humans
Clinical molecule was also used as a standard as a comparison

Gey L, Gernert M, Löscher W
Chronic focal delivery of the antiepileptic drug vigabatrin into the subthalamic nucleus (STN) for epilepsy treatment
Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie e.V. 80th Annual Meeting, April 1-3, Hannover, Germany.

COTE M.P., HOULÉJ. D.
Chloride cotransporter KCC2 is essential to exercise-dependent recovery of spinal reflexes after SCI.
Neuroscience 2013, San Diego, USA. November 9th - 13th 2013
http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=7fc906d1-b705-4ea2-9148-1668c789f104&cKey=87ddc290-d4ac-4e6e-8bca64232cf1e92c&mKey=%7b8D2A5BEC-4825-4CD6-9439-B42BB151D1CF%7d
Thank you for your attention.

Questions?