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Development of an implantable infusion pump for sustained anti-HIV drug administration

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Abstract

Factors such as insufficient drug potency, non-compliance and restricted tissue penetration contribute to incomplete suppression of Human Immunodeficiency Virus (HIV) and the difficulty to control this infection. Infusion via standard catheters can be a source of infection, which is potentially life threatening in these patients. We developed an implantable infusion pump, allowing to accommodate large volumes (16–50 mL) of high viscous solutions (up to 23.96 mPa s at 39 °C) of anti-HIV agents and providing sustained release of medication: a standard Codman® 3000 pump, which was initially developed to release aqueous solutions (∼0.7 mPa s) into the spinal cord such as for pain medication, was transformed for release of viscous solutions up to 40 mPa s by adapting the diameter of the capillary flow restrictor, the capillary length and way of catheterisation—by placing the indwelling catheter in the vena cava. A pilot study of the pump implanted in 2 dogs showed continuous steady-state release of the protease inhibitor darunavir (25 mg/dog/day administered for 25 days), thereby achieving plasma concentration levels of ∼40 ng/mL. Steady-state plasma levels were reproducible after monthly refill of the pumps.

In conclusion, the implantable adapted Codman® 3000 constant-flow infusion pump customized to anti-HIV therapy allows sustained release of anti-HIV medication and may represent an opportunity to reduce the pill burden and complexity of dosing schemes associated with common anti-HIV therapy.

Keywords: Infusion pump; HIV; Protease inhibitor; Darunavir; Experimental; Continuous infusion; Viscous solution; Codman® pump

1. Introduction

The treatment of Human Immunodeficiency Virus (HIV) infection remains a major medical challenge. HIV is able to evade immunological pressure, to adapt to a variety of cell types and growth conditions and to develop resistance against currently available drug therapies (Clotet, 2004; Simon et al., 2006). The current antiviral medications include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors (NTRTIs), HIV-protease inhibitors (PIs) and more recently, fusion-, entry- and integrase inhibitors.

Each of these drugs can only transiently restrain viral replication if used alone. This has led to the introduction of combination therapies combining several anti-HIV agents with a different activity profile (Clotet, 2004; Simon et al., 2006). The introduction of "HAART" (Highly Active Anti-Retroviral Therapy) has resulted in a significant reduction of morbidity and mortality in HIV patient populations (Palella et al., 1998). Current guidelines for antiretroviral therapy recommend such triple combination therapy regimen even for initial treatment (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents,

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2006). However, none of the currently available drug therapies is capable of completely eradicating HIV. Long-term treatment usually aims at suppressing virus replication maximally and durably and improving quality-of-life (Clotet, 2004; Simon et al., 2006).

The incomplete suppression of HIV can be attributed to insufficient drug exposure, poor adherence, restricted tissue penetration and drug-specific limitations within certain cell types (Clotet, 2004; Descamps et al., 2000; Kirschner and Webb, 1997; Ramírez-García and Côté, 2003). Known antiretrovirals, even when administered in a combination therapy regimen, have the common limitation that the HIV virus is able to mutate, changing thereby the targeted enzymes in the virus in such a way that drugs become less effective, or even ineffective against these mutant HIV viruses. The emergence of this ever-increasing resistance to medication may force physicians to increase the plasma levels of the HIV inhibitors in order to regain effectiveness of these inhibitors (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006).

Hence, anti-HIV treatment not only requires frequent intake of several medications, but also administration of relatively high doses, thus resulting in a highly undesirable "pill burden". An high pill burden increases the risk of non-compliance with the prescribed therapy, including HIV-infected individuals not taking the entire dose and/or not strictly adhering to the dosing frequency and times of intake. Both types of non-compliance reduce the effectiveness of the treatment and enhance the risk of inducing viral resistance to the medication (Kirschner and Webb, 1997; Fogarty et al., 2002; Clotet, 2004).

Yet another complicating factor in the medication regimen for the HIV-infected individual is that food can affect the absorption of anti-HIV medications from the gastro-intestinal tract. Food enhances the absorption for some drugs, while slowing it down for other agents (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006). This may prove to be particularly difficult, when administered in the combination treatment: the patient may need to take some of his medication in the absence of food while other medication must be taken in the presence of food.

Yet, adherence has been found critical to sustaining viral suppression in HIV treatment (Lucas et al., 1999; Sethi et al., 2003; Rathbun et al., 2005). There is thus a need for long-lasting HIV inhibitory therapy, avoiding a high pill burden and complex dosing schedules due to e.g. need for frequent drug intakes and food restrictions, and allowing dose reductions in comparison to current treatment: ideally, effects should be sustained over longer periods of time such as 1 week, one month or longer.

We describe the development of such implantable pump aimed at delivery of anti-HIV medication in the blood bed during at least one month and document its sustained delivery of darunavir (TMC114), a protease inhibitor with activity against a wide range of protease inhibitor resistant viruses (Koh et al., 2003), in a pilot study in dogs. The primary objective of this study in the dog was thereby to test the concept of using highly viscous solutions for anti-HIV drug administration after adaptation of an implantable pump system, so far only applied for administration of low-viscous solutions.

2. Methods

2.1. Pump selection

Codman® Model 3000 pumps (commercially available from Codman & Shurtleff of Raynham, Massachusetts, USA) were utilized. The Codman® 3000 pump is an implantable constant-flow infusion pump provided with a bolus safety valve (Codman® Model 3000 Series) that is currently available for intrathecal delivery of morphine sulphate for pain therapy or hepatic arterial infusion of chemotherapy at constant rate directly to the site of the tumor (http://www.Codman.com). These solutions are aqueous and have viscosities close to that of water, being 0.7 millipascal second (mPa s) or centipoise (cp).

The Codman® 3000 pump, presented in Fig. 1, is divided into an inner chamber and an outer chamber. The inner chamber, also known as the drug chamber is filled with the solution to be infused through the central port, which is made of self-sealing silicone with a needle stop, located below. The outer chamber contains a propellant that is located between the reservoir and the pump casing (Freon R-11). This propellant changes from a liquid to a gas at body temperature and exerts a constant pressure on the bellows (exterior surface of the reservoir). This forces drug solution through the filter, flow restrictor and catheter to the administration site. The pump contains a glass capillary flow restrictor tube with an internal diameter of 0.05 mm, cut to a calibrated length to achieve the target flow rate at the pump drive pressure of approximately 0.6 bar at 37 °C (Fig. 1). Temperature and pump pressure are directly proportional. The temperature and pump pressure are directly proportional. The impact of temperature on pump drive pressure and thus the flow rate is published in the Codman® 3000 instructions for use.

Different reservoir capacities are available (16, 30, and 50 mL) with preset flow rates varying from 0.5 to 3.4 mL/day. In this study, the existing pump for non-viscous solutions and human use was adapted for concept testing of delivery of a viscous solution of darunavir in the dog (see Section 2.5 for the viscous characteristics of the prepared solution, which was the

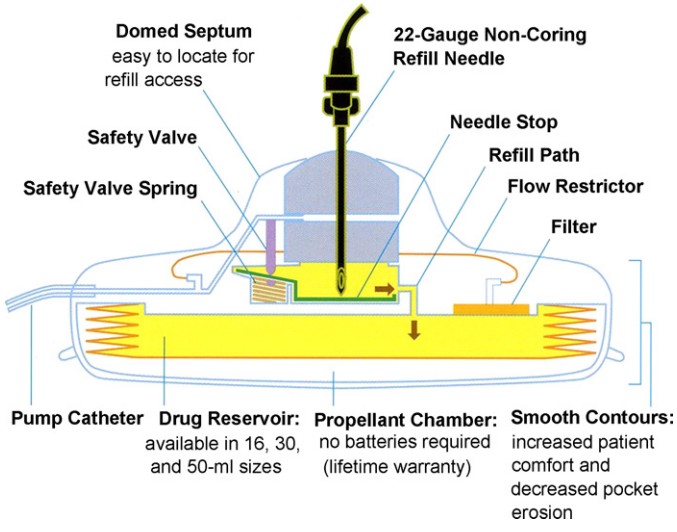

Fig. 1. Scheme of the Codman® Model 3000 pump.

starting point for the adaptation of the pump model in this study). It was decided to implant a 16 mL low-flow pump giving a nominal flow rate of 0.5 mL to cover a month delivery between pump refills.

2.2. Pump development and targeted adaptations

Two adaptations were targeted during the development of the pump: (1) constant delivery of highly viscous solutions (see darunavir solution, Section 2.5) and (2) delivery to the venous bed. As the design of the existing Codman® 3000 pump is suited for applications of aqueous solutions of relatively low viscosities (around 0.7 mPa s), the fine intrathecal catheter of the Codman® 3000 pump for intraspinal drug release was expected to restrict the outflow of the viscous solutions of anti-HIV medication. Therefore, increases in internal diameter glass capillary restrictor of the Codman® 3000 pump from the 0.05 mm standard diameter to 0.1 mm were tested and the length of the capillary was adapted to obtain the desired flow rate, in this case 0.5 mL/day at 39 °C in the dog with a TMC114 solution of a viscosity of 23.96 mPa s at this temperature. The capillary was thereby cut during manufacturing in order to achieve the targeted flow rate in the dog (the diameter was kept constant at 0.1 mm). Fluid viscosity and flow rate are thereby inversely proportional. Mathematically, the flow rate can be adjusted by changes in diameter and length of the glass capillary restrictor, according to Hagen–Poiseuille's law for non-turbulent flow of an incompressible or Newtonian fluid through a tube (Sutera and Skalak, 1993):

$$Q = \frac{\pi R^4 |\Delta P|}{8\eta L}$$

Q is the voluminal laminar flow rate, R is the radius of the capillary tube, ΔP is the pressure difference at the two ends of the capillary or drive pressure, η is the dynamic fluid viscosity and L is the length of the capillary tube. Thus, the desired flow rate for a particular fluid at a given temperature can be obtained by changing the radius or the length of the capillary tube. For the Codman® 3000 pump the radius is kept constant from a manufacturing supply-chain perspective and the length of the capillary tube is adjusted or cut to a calculated length (during manufacturing) that will provide the desired flow rate for that particular fluid, checked by a Codman® internal calibration procedure. It should be noted that, once manufactured, this is a constant-flow pump, i.e. the flow rate cannot be changed after manufacturing. The only method to adjust the dosage delivered is to change the concentration of the drug stored in the reservoir. Emptying the old solution from the pump and refilling it with a solution of the new concentration can achieve this desired change in dosage.

As previous applications made use of spinal or arterial administration, also adaptation for delivery in the venous bed was tested: in the case of pain therapy, the pump is only foreseen of a fine kink-resistant intraspinal catheter, too fine for outflow of viscous solutions; venous infusion is subjected to less pressure, with the additional advantage of release of the viscous drug solution in the direction of the blood stream. This way of administration was expected to be more suitable in order to achieve a constant outflow of viscous solutions from the larger capillary diameter.

2.3. In vitro testing of pumps

Prior to *in vivo* study, possible drug–container interactions were studied in a laboratory test. Pumps were filled with 16 mL of polyethylene glycol (PEG) 400 (pure, a darunavir solution or dilution) and stored for 32 days. Drug concentrations tested were as follows: darunavir in 70% PEG 400 (7 days), pure PEG 400 (17 days) and 70% PEG 400 (8 days). After completion of the experiment, the pump was sectioned for the purpose of visual examination. The compatibility study, performed by visual assessment after exposure of the pump to the active solution for 7 days, was considered to be sufficient, since no impact of the viscous solutions on the maintenance flow rate was detectable. Further since the objective of the study was primarily to assess whether viscous solutions could be delivered using modified implantable pumps, no in-depth analysis of impurities or pH was conducted at this stage of the research.

2.4. In vivo testing of pumps

In order to explore the utility of the Codman® pump for continuous anti-HIV drug delivery, the pumps were pre-filled with placebo (70% PEG 400) and implanted subcutaneously on the right flank of two male Beagle dogs. After implantation of the pumps, 25-day interval was respected before starting the experiments in order to allow full recovery of the dog's surgery before starting the experiments. Dogs were caged for the duration of the experiment as usual under standard conditions without food and drinking restrictions. Internationally accepted principles in the care and use of experimental animals were adhered to.

The solution (placebo or darunavir) was administered in the caudal vena cava via the indwelling catheter of the pump in the femoral vein. The targeted flow rate was 0.5 mL/day at 39 °C. The viscosity of the solutions was 23.96 mPa s at this temperature.

Each dog received 25 mg/day of darunavir over one-month periods. Pumps were refilled with maximum 16 mL of drug solution, depending on the volume to be replaced (as a function of time since last filling of the pump). Quantifying the refill volume as a function of time also enabled the veterinarian to measure the accuracy of the pump flow rate. Between experiments, pumps were refilled monthly (maximum 16 mL per refill) of placebo solution in order to avoid the pumps of running dry. Running dry of the pumps would introduce vacuum pressure, thereby allowing blood being pulled back into the capillary.

Plasma concentrations were studied during the first 25 days (Study 1). In two additional studies, the reproducibility of the pump outflow was tested after refilling the pumps with 16 mL of darunavir solution and dogs were monitored for plasma concentrations of darunavir for at least 15 days.

Blood samples (2 mL) were taken at fixed time intervals after initiation of the drug infusion of each applied treatment: at 8 h the first day of dosing and at 0, 4 and 8 h on the second and third

day of dosing (corresponding to 24, 28 and 32 h and 48, 52 and 56 h, respectively, after the start of the infusion study), and at 0 and 8 h on the fourth day (72 and 80 h, respectively, after start the of the infusion study) with repetition of the 0-h sampling every three days from day 5 onwards. This sampling schedule was re-applied following the refill of the pumps.

2.5. Protease inhibitors

Darunavir, or TMC114 is a protease inhibitor, which was in late phase III development stage at the time of testing and has recently been approved for oral administration in combination with low-dose ritonavir in several countries, including the USA and EU (Tibotec. PREZISTA™* (darunavir): Prescribing Information, June 2006).

Darunavir was dissolved in 56 mL of PEG 400 (a-Pharma, Belgium) under stirring overnight. Subsequently, 24 mL of sterile water (Braun, Belgium) was added under stirring to result in a mixture of 70/30% (w/w) PEG 400/water for injection. The solution was filtered over a 7 μm surfactant-free cellulose acetate (SFCA) membrane filter (Sartorius, Belgium) and 30 mL aliquots of the final solution were transferred into sterile vials (Medipac, Germany) for steam-sterilization (20 min at 120 °C) (Auto Koch Steam Sterilizer, pbi international, Italy) and administration. The final concentration in solution was equal to 50 mg/mL, to allow a daily administration of 25 mg/dog/day at a targeted outflow rate of 0.5 mL/day from the pump. Assessed with a Haake Rotovisco viscosimeter (Thermo Scientific), this test solution has a viscosity of 25.49 mPa s at 37 °C and 23.96 mPa s at 39 °C. The latter value was the start of the calculations for adaptation of the pump.

This viscous solution was proven to be stable over an 8 weeks period at 37 °C, its concentration at end of the stability testing ranging within 98 and 105% of the confidence limits of the labeled concentration.

2.6. Determination of drug concentrations

The concentration of darunavir in solutions was determined using a standard HPLC-analysis developed for darunavir by Tibotec, using a Merck Hitachi pump L7100, a UV detector L7400, an autosampler L7200 and an interface D7000 (Merck, Darmstadt, Germany). Peak areas were calculated using HSM software (Merck). Prior to analysis, samples for stability testing and content determination were diluted properly in methanol (Fisher Scientific, UK).

During the *in vivo* studies, blood samples (2 mL) were collected by vacutainer on EDTA as coagulator (EDTA Vacuette Greiner, Cat No. 454087). After sampling, blood samples were immediately placed on ice and plasma was obtained by centrifugation at 4 °C for 10 min (1900 × *g*). Plasma samples were transferred to the Bioanalytical Department for further storage in a freezer until analysis. Samples were stored at −18 °C or lower prior to analysis. At all times, blood and plasma samples were placed on melting ice and protected from light.

The plasma concentrations of unchanged darunavir were determined by means of a qualified research LC–MS/MS method. The lower limit of quantification for this method is 2 ng/mL in plasma samples. The plasma concentrations were expressed as mean values ± standard deviation (S.D.): all values taken during the study following the stabilization of the plasma concentration profile were included: this usually occurred within 1–2 days after refilling of the pump.

3. Results

3.1. Development of implantable pump for anti-HIV agents

Since the pump flow rate is inversely proportional to the solution viscosity, no flow was obtained with the original Codman® 3000 pump for the highly viscous darunavir solution. In order to enable its infusion, the diameter of the capillary flow restrictor was enhanced to 0.1 mm. Together with adapting the length of the capillary during manufacturing, this enabled a perfusion rate of 0.5 mL/day at 39 °C with the solution of the protease inhibitor darunavir, having a viscosity of 23.96 mPa s at 39 °C. This flow rate of 0.5 mg/day was confirmed by the *in vivo* test in the dog, by measuring the daily volume to refill the pump. Fig. 2 gives the technical specifications of the developed 16 mL Codman® 3000 implantable pump.

3.2. Laboratory study of drug–container interactions

Incubation of the pumps for 1 week at 37 °C with a solution of darunavir in 70% PEG 400 for 1 week, pure PEG 400 for 2 weeks, and 70% PEG 400 did not indicate any drug–container interactions. On visual examination of the dissected pump, no foreign build up on any of the components was visible at 10-fold or 50-fold microscopic magnification. Furthermore, no attack of the base material was found. There were no signs of any degradation of the materials, neither accumulation of the drug on the surface of the pump bellows. All materials withstood the exposure with no anomalies due to reaction with the drug concentrations observed.

3.3. Experimental pilot study

Fig. 3 depicts the plasma concentration profile of darunavir given as a continuous infusion over 25 days with the pump implanted in the flank of 2 dogs. The plasma concentration profile of darunavir in the 2 dogs essentially immediately attained steady-state, with an average concentration of 40 ng/mL for both dogs. Apart from an initial peak in one dog, presumably related to a transient increase in pump pressure during filling, the variability in plasma concentration levels between the 2 dogs was limited.

The mean steady-state plasma concentrations of darunavir and extremes, measured from day 2 onwards after refilling the pumps, are listed in Table 1 for the 3 experiments. They confirm the reliability of the pump system (Fig. 4).

Pump materials:	**Titanium/Silicone rubber**
Weight (empty):	**98 g**
Septum target diameter:	**10.2 mm**
Septal height:	**12.3 mm**
Body height:	**19.7 mm**
Overall height:	**32.0 mm**
Overall diameter:	**61.2 mm (excluding loops)**
Reservoir volume:	**16.0 mL**
Catheter size:	**0.6 mm ID x 2.3 mm OD x 50cm long, silicone rubber with 3 suture beads**
Catheter volume:	**0.15 mL (50 cm) or 0.003 mL/cm**
Flow rate:	**Preset constant flow**

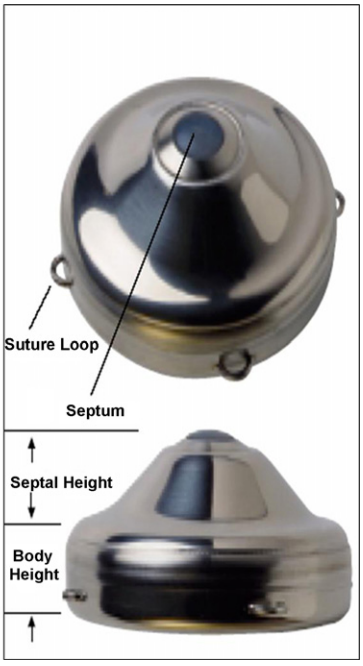

Fig. 2. Technical specifications of the 16 mL Codman® 3000 implantable pump ID = inner diameter, OD = outer diameter.

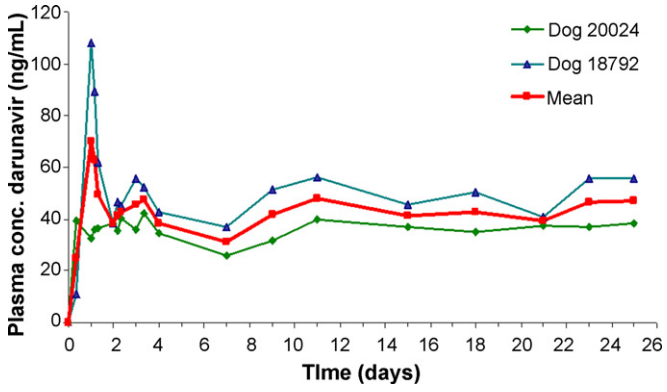

Fig. 3. Plasma concentration profile of darunavir given as a continuous infusion at constant rate (25 mg/dog/day) for ~4 weeks in 2 dogs implanted with an adapted Codman® 3000 pump: mean and individual values in 2 dogs.

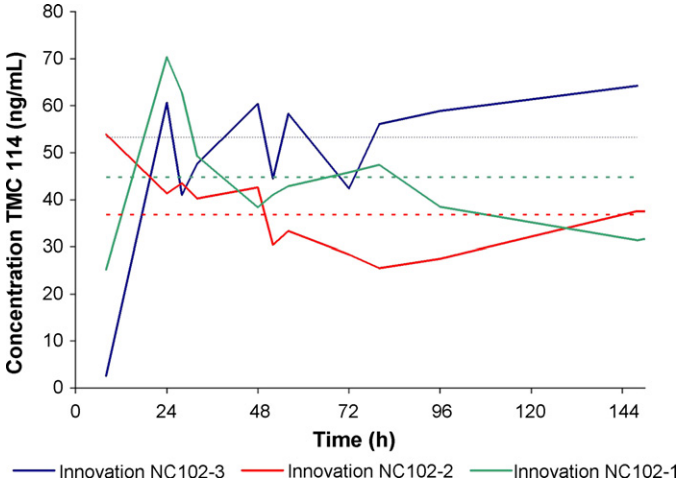

Fig. 4. Reproducibility of the plasma concentration profile obtained with darunavir continuous infusions (25 mg/dog/day) in 2 dogs implanted with an adapted Codman® 3000 pump: mean values of the plasma concentration profile in 2 dogs measured during at least 6 days following refilling of the pumps with darunavir solution. Innovation NC102-1, -2 and -3 refer to Study 1, 2 and 3, respectively.

Table 1
Reproducibility of release rates of the protease inhibitor darunavir dosed at 25 mg/dog/day during continuous infusion from an adapted Codman® 3000 pump implanted in 2 dogs: mean plasma concentrations and range of observed individual data per dog*

	Duration observation (days)	Plasma concentrations (ng/mL)*			
		Mean (S.D.)		Extremes of observed individual data	
		Dog 1	Dog 2	Dog 1	Dog 2
Study 1	25	36.3 ± 3.8	51.6 ± 12.4	25.9–42.4	36.8–89.3
Study 2	16	36.6 ± 1.7	50.8 ± 6.3	34.8–40.0	40.0–56.0
Study 3	6	39.6 ± 8.5	65.6 ± 9.5	28.1–48.6	53.9–80.6

* Excluding outlier values during day 1 and/or 2 following the refilling of pump with darunavir solution. Outlier plasma levels (spikes in plasma concentration levels eventually seen on day 1 and 2 due to a transiently increased pressure after filling of the pump) were identified by visual inspection of the data.

4. Discussion

Antiretroviral treatments have given hope to people living with HIV/AIDS and play a role in improving their quality-of-life (Ramírez-García and Côté, 2003; DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006). However, the effectiveness of these treatments is directly related to the level of adherence and commitment to them (Lucas et al., 1999; Fogarty et al., 2002; Clotet, 2004; Sethi et al., 2003; Ramírez-García and Côté, 2003; Rathbun et al., 2005; DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006). Many factors play a role in adopting and maintaining adherence behaviour so that it is highly desirable to develop reliable dosage systems for administering HIV inhibitors such as an implantable pump.

The presented implantable pump to administer anti-HIV medication would allow to reduce both pill burden and complexity of dosing schemes associated with common anti-HIV therapy. The pump is surgically implantable in the body and has an outlet catheter with the proximal end fluidly connected to the pump and a distal end fluidly to be connected to the desired vessel in the patient's body. The pump consisting of an inner chamber, which contains the drug to be infused, can also easily be refilled externally at defined and long-time intervals, such as one month or longer, so that the patient no longer has to worry about complicated drug regimens in the period in between. The pump can be refilled by injection through the skin into an appropriate septum: the large, domed, single-septum access of the pump allows easy access for bolus procedures and refill of the reservoir. Moreover, the pump design allows secure needle retention for bolus injections, thereby minimizing the risk for infections in the HIV patient who is at high risk of this life-threatening complication. The pump has smooth contours for patient comfort. As the pump is totally implantable, it also allows patients to move freely around.

The pilot study showed that the implanted pump could be used to release protease inhibitors such as darunavir, at a sustained constant rate. An advantage is the immediate establishment of steady-state levels. In humans, oral darunavir, in combination with ritonavir (600 mg/100 mg twice daily), has been shown to be effective in patients who failed on ritonavir-boosted protease inhibitor regimens (Poveda et al., 2006). Hence, the observations with the implantable pump in the dog are not only relevant from a pharmacokinetic and pharmacodynamic standpoint for human implementation. It is also expected that this experimental set-up using an implantable pump can be used as a reliable, sensitive test system for detection of boosting effects on co-administration of anti-HIV agents.

Although only 2 dogs were studied for ethical reasons in this concept study and thus statistics could not be applied, the plasma concentration profiles indicated only limited variability in plasma concentration levels within and between the dogs. Previous studies with oral darunavir in dogs have shown highly variable plasma concentrations after oral administration (Lachau-Durand et al., 2005).

Administration of anti-HIV medication via a pump can confer several benefits for patients in clinical practice. While with oral medication, there is no guarantee that patients will take all the tablets needed to assure an effective dose, the implantable pump guarantees continuous delivery of the HIV inhibitory agents so that effective blood plasma levels are being provided over long periods of time. When drug concentrations are kept stable above minimum inhibitory levels, below which the virus is able to mutate, this should substantially reduce the risk for inducing resistance. For oral regimens, the liability is largest at the time of pharmacokinetic troughs, the minimal plasma concentrations within the oral dosing intervals. Next to elevating troughs, the obtained pharmacokinetic profile suggests also reduction of the peaks in plasma levels, associated with intake of oral medication, thereby potentially reducing side effects associated with high peak plasma levels.

Other important advantages of the implantable pump are the lack of passage through the gut, thereby avoiding interactions of the drug with the gastro-intestinal system, drug–food interactions, hampered transfer through the intestinal membrane, decomposition in the stomach and liver-related first-pass metabolism. At least for pain treatment with opioids, the use of pumps has enabled to enhance response rates and efficacy of treatment, dose reductions, reductions in side effects associated with therapy and improvement in activities of daily living and quality-of-life (Lamer, 1994; Portenoy, 1994; Dougherty and Staats, 1999; Winkelmüller and Winkelmüller, 1996). Thus, the use of an implantable pump for delivery of anti-HIV medication warrants further investigation for human use.

It is also expected that the pump can reliably release other HIV inhibitory agents or combinations. As the anti-HIV compounds can be administered as a combined preparation for simultaneous administration, or separately for sequential administration, this pump opens an array of potential applications in the future for targeted delivery of the anti-HIV agent directly to in the body.

In conclusion, the implantable pump described allows constant sustained delivery of anti-HIV medication. This will not only lead to reduced pill burden for the patients, but also will allow better control of the drug plasma concentrations, as plasma levels can be kept stable, avoiding high plasma peaks associated with side effects, while maintaining safe minimum plasma concentration levels above those at which the virus is able to mutate.

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