Ciprofloxacin PulmoSphere® Inhalational Powder: a healthy volunteer study

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Revised abstract

Introduction: *Pseudomonas* spp. often colonize the lungs of patients with cystic fibrosis (CF); ciprofloxacin has proven antipseudomonal activity. An inhaled formulation of ciprofloxacin – Ciprofloxacin PulmoSphere® Inhalation Powder (CPIP) – in combination with a small portable dry powder inhaler, is designed to maximize bactericidal activity at the lung epithelium. CPIP is in development for the treatment of chronic lung infection in CF patients.

Methods: This single-center, randomized, single-blind, placebo-controlled, 2-fold cross-over study, investigated the safety, tolerability and pharmacokinetic (PK) properties of CPIP in 6 healthy male subjects, aged 27–42 years. Subjects inhaled a single dose of 50 mg CPIP (~32.5 mg ciprofloxacin betaine) or 40 mg placebo. Safety parameters included: vital signs, ECG, laboratory tests, adverse events and lung function (total specific resistance, thoracic gas volume, and FEV_1). Systemic distribution (plasma and urinary) of ciprofloxacin was monitored. Plasma vs time concentrations were used to calculate PK parameters. A physiological PK model of inhalational administration (PK-Sim®) was developed and used to estimate deposition of CPIP in the lung.

Results: CPIP was well tolerated. Lung function studies found no clinically relevant adverse effect of CPIP. Total systemic exposure was minimal (AUC 0.354 mg*h/L, median t_{max} 0.6 h; C_{max} 0.06 mg/L) vs historic data after a single IV or PO administration (e.g. C_{max} 3–5 mg/L). Terminal half life (9.5 h), clearance (91.7 L/h) and volume of distribution (1262 L) data indicate that lungs are a target organ for this inhaled drug. PK-SIM® showed that about 20% of the inhaled dose is deposited in the trachea/bronchi.

Conclusion: In healthy subjects, inhaled ciprofloxacin results in minimal systemic exposure, delivers active drug to the lungs, and is well tolerated.

Introduction

- Patients with cystic fibrosis (CF) have reduced mucociliary clearance, leaving them susceptible to endobronchial infections.[1]
- Colonization by *Pseudomonas aeruginosa* is common in CF patients and leads to an increased rate of disease progression.[2,3] It is also a significant predictor of mortality.[4]
- Nebulized tobramycin and colistin therapies (which are currently used to target drugs to the lung epithelia) can be time-consuming and inconvenient.[5] Furthermore, nebulized colistin has not been shown to improve lung function.[6]
- The fluoroquinolone, ciprofloxacin, has proven antipseudomonal activity,[7] and hence the potential to reduce the incidence of chronic airway infections. In turn, this may contribute to improvements in long-term prognosis.
- An inhalation form of ciprofloxacin – Ciprofloxacin Pulmosphere® Inhalation Powder (CPIP) – for use in combination with a small, portable dry powder inhaler has been developed specifically to improve the treatment of CF while minimizing the delivery time burden.
- PulmoSphere® powder and inhalation device technologies (Nektar, San Carlos, CA, USA) allow control over the size, density and morphology of the particles produced and are, therefore, optimized for the pulmonary delivery of ciprofloxacin to patients with CF.

Objective

- To investigate the safety, tolerability and pharmacokinetic (PK) properties of CPIP when given as a single inhaled dose to healthy volunteers.

Study design and methods

- This was a Phase I single-center, randomized, single-blinded, placebo-controlled, two-fold crossover study conducted in healthy male subjects.

Study drug formulation and dosage

- CPIP was manufactured using an emulsion-based, spray drying process that creates highly dispersible, low density particles with mass median aerodynamic diameters of <5 µm.[8]
- CPIP was inhaled from T-326 Nektar inhalers (Bayer HealthCare AG, Germany) (Figure 1). Capsules were filled with 50 mg of powder containing an active dose corresponding to 32.5 mg ciprofloxacin betaine; placebo doses of powder were given in identical capsules.

Study procedures

- Healthy subjects received a single inhalational dose of 32.5 mg ciprofloxacin betaine as CPIP followed by a corresponding dose of placebo treatment after a washout period of at least 1 week.
- Safety and PK parameters were measured at baseline and at regular intervals for 48 h after study drug administration.
- Safety evaluation parameters included vital signs, electrocardiogram, lung function (total specific resistance, thoracic gas volume [TGV] and forced expiratory volume in 1 sec [FEV_1]). PK evaluation parameters were drug concentrations in blood and urine samples.

Analyses

- Quantitative analysis of ciprofloxacin was performed using a validated HPLC/MSMS (plasma) or HPLC assay with fluorescence detection (urine).
- Plasma ciprofloxacin concentrations were determined by mass spectrometry.
- PK parameters were calculated from the plasma concentration versus time data using the model-independent compartment-free method using WinNonlin 4.1a (Pharsight Corporation, Mountain View, CA, USA).
- A physiological PK model of inhalational administration (PK-Sim®) was developed and used to estimate CPIP deposition in each patient. Total deposition and deposition in each of the oral cavity, alveolar space and trachea/bronchi were estimated.

Results

- Six healthy male volunteers were recruited to the study. Subjects' baseline demographics are shown in Table 1.

Table 1 Summary of demographic data at baseline (N=6)

Parameter	Value
Age (years) (mean [range])	32.8 (27–42)
Race, white (n)	6
Male subjects (n)	6
Weight (kg) (mean [SD])	80.2 (13.3)
Height (cm) (mean [SD])	178.5 (6.2)
BMI (kg/m^2)	25.1 (3.6)

SD: standard deviation; BMI: body mass index

Pharmacokinetics

- Rapid systemic uptake of ciprofloxacin occurred after a single dose. After reaching the peak at 15 min, CPIP concentrations remained stable until approximately 1–1.5 h after inhalation (Figure 2) and then slowly declined ($t_{1/2}$ = approximately 9.5 h) (Figure 3).
- Derived PK parameters are shown in Table 2.

Figure 1 T-326 Nektar inhaler

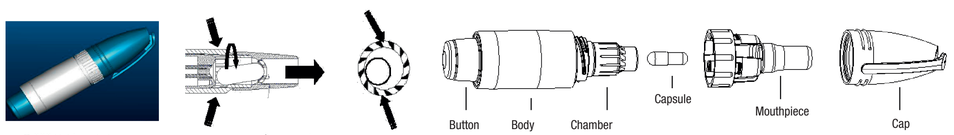


Figure 2 Geometric mean (solid curve) and individual (dotted curves) plasma concentration versus time courses of ciprofloxacin following a single inhaled dose of Ciprofloxacin Pulmosphere® Inhalation Powder up to 6 h after administration (N=6)

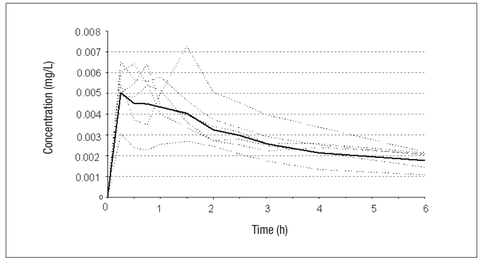


Figure 3 Geometric mean (standard deviation) plasma concentrations of ciprofloxacin following a single inhaled dose of Ciprofloxacin Pulmosphere® Inhalation Powder (N=6)

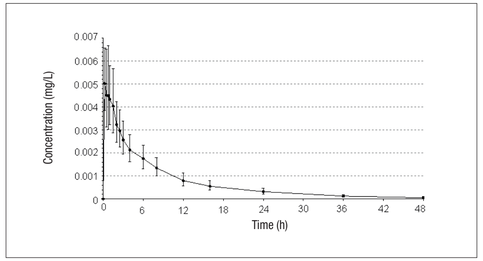


Table 2 Plasma pharmacokinetic parameters of ciprofloxacin following a single inhalation dose of 32.5 mg ciprofloxacin betaine as Ciprofloxacin Pulmosphere® Inhalation Powder (N=6)

Parameter	Geometric mean/CV	Range
AUC (mg*h)/L	0.354/30.3	0.21–0.46
AUC_{norm} (kg*h)/L	0.86/41.8	0.45–1.38
AUC/D (h/L*10^{-3})	10.90/30.3	6.45–14.09
C_{max} (mg/L)	0.056/32.2	0.031–0.073
t_{max} (h)†	0.63	0.25–1.50
$t_{1/2}$ (h)	9.54/19.7	7.32–12.91
MRT (h)	10.68/14.8	8.82–13.34
V_z/f (L)	1262/33.2	951–1969
CL/f (L/h)	91.71/30.3	70.97–155.0

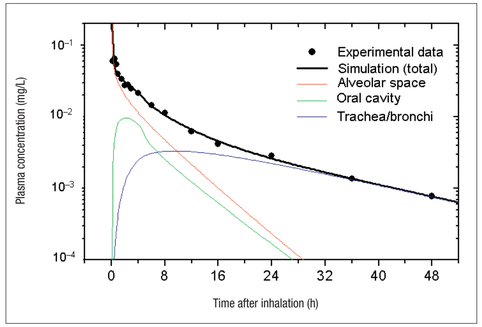
†Median
CV = Geometric coefficient of variation; AUC = area under the curve; AUC_{norm} = area under the curve divided by dose per kg body weight; AUC/D = AUC divided by dose (mg); C_{max} = maximum concentration; t_{max} = time to reach maximum drug concentration in plasma after a single dose; MRT = mean residence time; V_z/f = apparent volume of distribution; CL/f = total body clearance from plasma after nonsystemic administration

- Systemic exposure to ciprofloxacin was considerably lower when compared with oral systemic data (e.g. AUC 0.35 vs 16.8 mg*h/L for 32.5 mg inhaled vs 750 mg oral dose).[9]
- The half-life of >9 h following inhalation of the 32.5 mg dose is considerably greater than oral systemic data (4–6 h).[9]

Lung deposition: results of physiological modeling

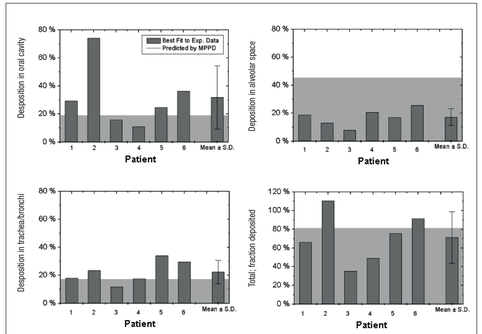
- Physiologically based PK (PBPK) modeling confirmed slow clearance of a portion of the dose by mucociliary clearance from the broncho-tracheal tract (Figure 4).

Figure 4 Physiological modeling of ciprofloxacin in the oral cavity, alveolar space and trachea/bronchi following a single inhalational dose of 32.5 mg ciprofloxacin betaine as Ciprofloxacin Pulmosphere® Inhalation Powder



- According to a PKSim® model, mean CPIP deposition in the trachea/bronchii was 20%, with moderate variability (Figure 5).

Figure 5 Percentage deposition of ciprofloxacin in the lung compartments following a single inhalation dose of 32.5 mg ciprofloxacin betaine as Ciprofloxacin Pulmosphere® Inhalation Powder



S.D. = standard deviation; MPPD = multiple path particle dosimetry

Safety

- No serious or significant adverse events were reported. One transient adverse event (dysgeusia) occurred in five subjects (ciprofloxacin, n=4; placebo, n=1). In all cases, this resolved within 30 min.
- Lung function parameters (total specific resistance, thoracic gas volume and FEV_1 remained virtually unchanged in five of the six subjects. One subject experienced a transient reduction in FEV_1 values (<50% by verum) that returned to baseline without the need for intervention.
- Overall, there were no changes in lung function parameters indicative of any clinically relevant adverse effects of ciprofloxacin betaine administered as a dry powder formulation.

Conclusion

- A single inhalation dose of 32.5 mg ciprofloxacin betaine as CPIP was safe and well tolerated in healthy male subjects 27–42 years of age without affecting lung function.
- CPIP was targeted effectively to the lungs, as calculated from PK data using PBPK methods.
- Ciprofloxacin in plasma has a prolonged half-life due to slow clearance from the broncho-alveolar space.
- The pulmonary targeting and low systemic exposure of inhaled CPIP suggests it may be an excellent candidate for the treatment of *P. aeruginosa* infections in CF patients.

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