Pharmacokinetics and Safety of Pirfenidone Following Inhaled Delivery to Sheep: A Viable Approach to Treating Idiopathic Pulmonary Fibrosis

M. Surber[1], L. Kaminskas[2], C. Landersdorfer[3], R. Bischof[4], S. Beck[1], S. Pham[1], A. Jain[5], A. Halvarsson[5], M. Hug[5], A. Montgomery[6]

[1]Avalyn Pharma, Inc., San Diego, CA, United States, [2]School of Biomedical Sciences, University of Queensland, St. Lucia, Australia, [3]Centre for Medicine Use and Safety, Monash University, Parkville, Australia, [4]Hudson Institute of Medical Research, Clayton, Australia, [5]PARI Pharma, GmbH, Gräfelfing, Germany, [6]Avalyn Pharma, Inc., Seattle, WA, United States.

ABSTRACT

RATIONALE: Inhaled delivery of pirfenidone (PFD) directly to lungs of idiopathic pulmonary fibrosis (IPF) patients holds promise to eliminate oral-observed side effects while enhancing efficacy. This study aimed to comprehensively describe the pulmonary pharmacokinetic behavior of PFD.

METHODS: PFD concentrations in plasma, lung-derived lymph and bronchoalveolar lavage (BAL) fluid were evaluated after nominal inhaled delivery of 119 mg PFD (in vitro nebulizer device simulation predicted 49 mg lung-delivered dose) to healthy adult sheep. Respiratory parameters were measured at the completion of aerosol delivery and showed no changes in baseline respiratory function following aerosol delivery.

RESULTS: Pulmonary bioavailability of PFD was calculated to be 102 ± 18% by comparing the PFD plasma concentration-time profile after aerosol delivery to that in the same sheep after IV infusion. Urea-corrected BAL fluid analysis paired with compartmental pharmacokinetic evaluation indicated that a 49 mg PFD lung-deposited dose delivered an epithelial-lining fluid Cmax and AUC of 62 ± 23 mg/L and 21 ± 5 mg·h/L, respectively. Plasma concentrations from these sheep exhibited a Cmax and AUC of 3.5 ± 1.0 mg/L and 1.6 ± 0.4 mg·h/L, respectively. Further analysis revealed that plasma PFD reached Tmax more quickly and at higher concentrations than in lymph. These results suggested inhaled PFD was cleared from the alveolar interstitium via blood more rapidly than PFD could equilibrate between the lung interstitial fluid and lung lymphatics. Interestingly, while the plasma profile after inhaled delivery exhibited 2-compartmental elimination pharmacokinetics, lymph fluid exhibited 3-compartmental elimination pharmacokinetics, suggesting a non-alveolar 'pool' of PFD feeds into lung lymph at later time points (after PFD has largely been cleared from plasma), providing for prolonged lung lymphatic exposure of the drug.

CONCLUSION: This study indicates inhaled pirfenidone efficiently deposits in epithelial-lining fluid and is cleared from the lungs by initial absorption into plasma, followed by later equilibrium with lung interstitial and lymph fluid.

OBJECTIVES

- Determine inhaled PFD pharmacokinetics in a large animal model
- Characterize inhaled PFD pulmonary elimination
- Create a sheep ELF standard curve to estimate human ELF PK

MATERIALS AND METHODS

Sheep and surgeries
- 1-2 yr old Merino cross-bred ewes (32 to 40 kg; mean 35.7 kg)
- Lung lymphatic, jugular vein and carotid artery cannula placements described elsewhere (1)
- All procedures approved by Monash University Animal Ethics Committee and conducted in accordance with Australian Code of Practice for the Care and Use of Animals for Scientific Purposes

Dosing
- Intravenous dosing (12.3 mg/mL pirfenidone) via ~60 min infusion to a jugular vein cannula (0.58 mL/min), followed by 10 mL heparinized-saline flush
- Inhaled dosing (14.9 mg/mL pirfenidone) via the eFlow® Inline nebulizer (PARI Pharma GmbH) placed in-line with a dual phase control respirator (Harvard Apparatus, MA, USA), providing a closed respiratory loop with a nasal-inserted endotracheal tube (1). 20 breaths/min and 50% inspiration. Doses delivered over ~12-21 min

Sampling
- Peripheral blood and lymph collected from cannulated jugular vein and cannulated efferent caudal mediastinal lymph node (CMLN)
- BAL collected from separate lung segments via bronchoscope (20 mL infused, ~3-13 mL recovered). Samples collected from separate lung segments/lobes to avoid contamination/dilution (2)

Pharmacokinetic analysis
- Non-compartmental analysis by standard techniques [what techniques/software?]
- Compartmental analysis by nonlinear mixed-effects modelling of population pharmacokinetics following inhaled administration performed utilizing the S-ADAPT platform (version 1.57) with the Monte Carlo parametric expectation maximization algorithm (importance sampling, pmethod=4) (3). The SADAPT-TRAN program was used for pre- and post-processing (4,5)

RESULTS

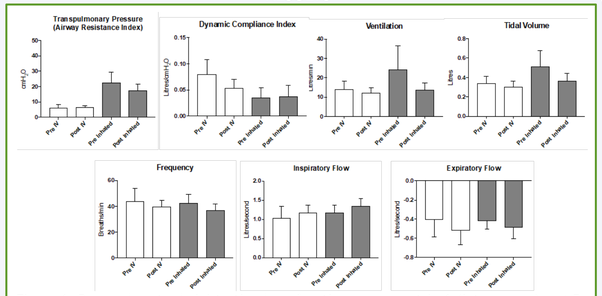


Figure 1. Pre- and post-administration lung function assessment in 6 (intravenous) and 5 (inhalation) sheep. There were no significant changes (pre- vs post-) seen in the mean airway resistance, dynamic compliance, ventilation, tidal volume, frequency of breathing, or inspiratory or expiratory flow in sheep following either the intravenous or inhaled pirfenidone administration. Data depicted as mean ± SEM

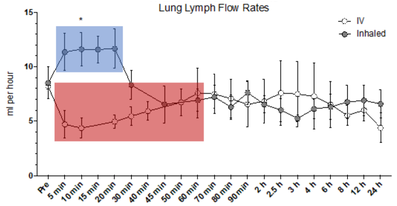


Figure 2: Lung lymph flow rates from initiation of intravenous and inhaled pirfenidone administration through 24 hrs. Red (intravenous; 59.6 ± 0.7 min) and blue (inhalation; 16.9 ± 0.9 min) boxes depict dosing period (mean ± SEM). Y-axis depicts mean flow rate ± SEM for n = 6 (intravenous) and 5 (inhalation) sheep

Table 1. Inhaled pirfenidone plasma and lymph pharmacokinetic parameters in sheep

				Sheep Number				
PK Param	**Mean**	**SEM**	**Units**	**S5**	**S7**	**S9**	**S11**	**S12**
Plasma								
AUC	1.56	0.38	mg·h/L	1.26	0.93	0.90	2.95	1.77
F_{abs}	1.02	0.18	-	1.13	0.83	0.63	3.43[a]	1.47
K_{alpha}	3.11	0.56	h^{-1}	2.23	3.15	3.40	1.76	5.03
K_{beta}	1.01	0.11	h^{-1}	1.05	1.00	1.36	0.66	0.96
Initial $T_{\frac{1}{2}}$	0.25	0.04	h	0.31	0.22	0.20	0.39	0.14
Terminal $T_{\frac{1}{2}}$	0.73	0.09	h	0.66	0.69	0.51	1.05	0.72
C_{max}	3.50	0.96	µg/ml	2.09	1.87	2.05	6.58	4.95
T_{max}	0.25	0.05	h	0.33	0.25	0.25	0.08	0.33
Lung Lymph								
AUC	1.32	0.09	mg·h/L	1.47	1.30	1.42	0.99	1.43
K_{beta}	0.26	0.05	h^{-1}	0.22	0.16	0.21	0.26	0.46
Terminal $T_{\frac{1}{2}}$	3.0	0.5	h	3.1	4.4	3.3	2.7	1.5
C_{max}	1.76	0.07	µg/ml	1.68	1.69	2.04	1.77	1.64
T_{max}	0.33	0.00	h	0.33	0.33	0.33	0.33	0.33

a. An outlier resulting from unusually high plasma concentrations after inhaled dosing compared to other sheep. This data point was excluded from the bioavailability calculation

RESULTS

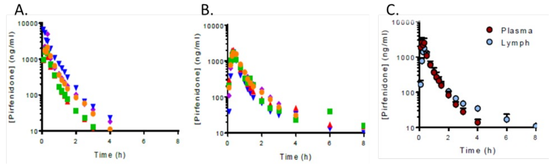


Figure 3. Pirfenidone plasma (panel A) and lung lymph (panel B) concentrations in individual sheep and mean [is 'mean' correct?] plasma and lymph overlay (panel C; ng/mL ± SEM). Time initiates at start of inhaled administration

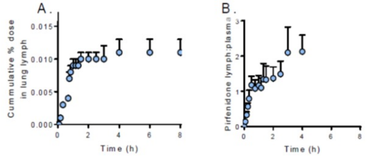


Figure 4. Inhaled pirfenidone lung lymph cumulative percent dose (panel A) and lung lymph to plasma ratio (panel B). Time initiates at start of inhaled administration

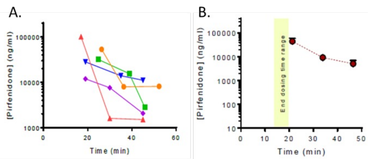


Figure 5. Pirfenidone concentrations in lung epithelial lining fluid (ELF) in individual sheep (panel A) and mean [is 'mean' correct?] (panel B) after inhaled aerosol administration. Concentrations in ng/mL ± SEM. Time represents duration after the start of inhaled administration

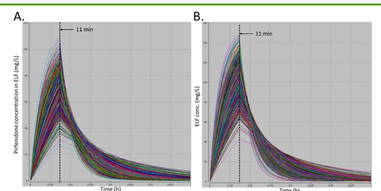
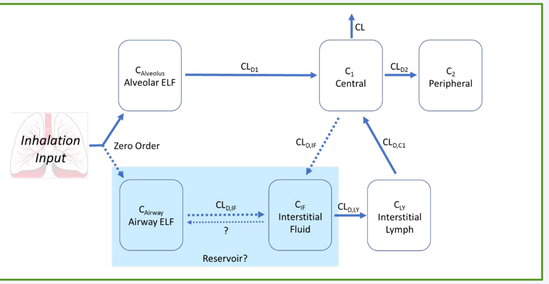


Figure 6. Pirfenidone ELF concentrations in 1000 virtually-simulated sheep. 49 mg pirfenidone inhaled and deposited dose delivered over 11 min. All sheep predicting 5th, 50th and 95th percentile C_{max} as 50, 70 and 90 µg/mL, respectively (Panel A) and excluding one sheep (outlier plasma:ELF ratio) predicting 5th, 50th and 95th percentile C_{max} as 72, 103 and 131 µg/mL, respectively. In all cases, the mean pirfenidone ELF elimination half-life was X min (range Y to Z min). Data incorporates all sheep (Panel B)

PIRFENIDONE PHARMACOKINETIC MODEL



PHARMACOKINETIC SUMMARY

Plasma and lymph:
- Inhaled PFD deposited in the lung via zero order kinetics
- Deposited PFD rapidly eliminates from alveolar regions to central circulation
- Lymph T_{max} was delayed vs. plasma with a longer terminal half-life; suggesting an additional reservoir
- Non-alveolar airways may be the reservoir feeding interstitial fluid and lung lymph:
  - Alveolar absorption is primarily vascular and non-alveolar regions is primarily lymphatic (6,7)
  - While a substantial portion of inhaled PFD aerosol particles were small enough to deposit in alveolar regions, a portion of larger inhaled particles will deposit in middle airways

Lung ELF:
- ELF levels indicated a high initial pirfenidone concentration followed by rapid absorption
- Due to rapid absorption and delayed sampling, ELF Cmax could only be estimated (true Cmax at end of dose)

Compartmental modeling:
- Indicated true sheep ELF Cmax was between ~62 and ~103 µg/mL, with a 7 min initial half-life
- Comparing human-obtained PFD ELF data (8) suggested the Figure 6B model may be most accurate
- Using the Figure 6B model as a standard curve and extrapolating human ELF data back to end of dose indicated the true human ELF C_{max} may be ~136 µg/mL

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