Pharmacokinetic prediction of nebulised polymyxin for pulmonary delivery

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Abstract: Inhaled administration of polymyxin B is increasingly used to treat multi-drug resistant bacterial lung infections. However, the lack of clinical data on the pharmacokinetics of inhaled administration makes drug dose design, efficacy assessment and drug safety assessment a challenge. In this study, clinical data from intravenous injections were deconvoluted by an equal-step numerical deconvolution algorithm to derive the drug absorption rate of polymyxin B in vivo. The absorption rate was substituted into a published pulmonary absorption compartment model to predict the systemic pharmacokinetics of polymyxin B. It was demonstrated that the intravenous PK dataset with the pulmonary compartment model provided reliable estimates of the accuracy and bias of inhaled systemic pharmacokinetics.

1. Introduction

Antibiotic resistance has never been addressed since the inception of antibiotics. In 2017, the World Health Organization made antibiotic resistance a very prominent issue on its list of priority pathogen. Unfortunately, drug development can not keep up with the demand for new antibiotic drugs. Some abandoned antibiotics such as polymyxin received renewed attention for clinical treatment. In 2021, China bacteria resistance detection(CHINET) showed the resistance rate of A. baumannii and found that only colistin drugs have better activity. Three forms of colistin are mainly used clinically in China: polymyxin B sulfate、colistin sulfate、 colistin methanesulfonate sodium (CMS). Polymyxin B sulfate is used only in China, relevant clinical data is therefore lacking. There are two CMS products available nationally, from Europe and the United States, with different dose definitions for the two products. Polymyxin B and Colistin differ in chemical structure by only one amino acid, and they are very similar in pharmacology. Polymyxin B and colistin are positively charged. After being filtered through the glomerulus in the kidney, the concentration of the positively charged molecules inside the cells is 2,000 to 5,000 times higher than outside cells[1]. CMS is an active drug precursor that is converted to the active drug colistin in vivo. Negatively charged CMS had stronger exudation in the tubular epidermal cells after filtration and therefore higher amounts of CMS in the urine[2]. However, CLSI has removed the colistin inflection point because intravenous, subcutaneous, and intramuscular injections were found to be less effective in the treatment of lung infections based on mouse lung models. This result is inappropriate in terms of PK and PD because the exposure of injectable colistin in the lung is low, while the drug can be delivered to the lung in large quantities by inhalation and the inflection point may be high. From the perspective of PK and PD, inhalation is a relatively advantageous delivery method for the treatment of pulmonary infection. However, there are few clinical data on colistin inhalation to obtain accurate PK values. Therefore, it is important to use pharmacokinetic models to predict the blood-concentration of polymyxin. Predicting the pharmacokinetic models of inhaled drugs can be used for drug dose design, efficacy assessment and drug safety assessment, which have important clinical significance. Pharmacokinetic modeling requires the use of experimental data to establish pharmacokinetic models of inhaled drugs by parameter estimation and other methods and then predict the concentration changes of drugs in the body[3].

In this study, the distribution of colistin in next generation impactor (NGI), particle size distribution generated by atomization and other data will be combined to determine the relationship between drug absorption, blood drug concentration, and finally estimate the PK of atomized polymyxin in human body.

2. materials and methods

2.1 Materials

Polymyxin B sulfate was purchased from Borui Biotechnology Co., Ltd. (Suzhou City, Jiangsu Province, China). Mesh nubelizer was purchased from Yuwell

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Medical equipment Co., Ltd. (Suzhou City, Jiangsu Province, China). High performance liquid chromatography (HPLC) grade was supplied by Jiangsu Provincial Industrial Process Research Institute. Polymyxin B was dissolved to a solution of 5 mg / mL in Milli-Q water.

2.2 Particle Size Distribution

Laser diffraction particle sizer (HELOS&INHALER, SimpaTic Corporation, Germany) was used to measure the particle size distribution. The Sympatec HELOS system in the inhaler module is tested by laser diffraction scattering particle size distribution measurement. Particle size in 10%, 50% and 90% of the obtained cumulative particle size distribution curve of the volume reference are taken as 10% particle size (D10), (D50) and (D90), respectively[4].

2.3 Aerodynamic Properties

Next generation impactor (NGI) (Copley Science, Nottingham, UK) consisting of 7 impact steps and a micro hole collectorwas was used to determine the aerodynamic properties of the composite formulation. Before the measurement, impact plates were sprayed with silicone oil to fix particles. Critical flow controller (Erweka, Heusenstam, Germany) was used to maintain the flow at 15L/min and duration is 120 seconds. HPLC was used to determine the drug content at each stage, and the data processing software CITDAS (Copley Sciences, Nottingham, UK) was used to calculate the fine particle fraction (FPF) and median mass aerodynamic diameter (MMAD) [5]. Relevant data was used as an input to estimate the pulmonary delivered dose and the central/peripheral deposition ratio.

2.4 Estimating the Drug Absorption

Numerical deconvolution method was used to deconvolute the plasma PK profiles. The drug absorption rate of polymyxin B after inhalation was deconvoluted by utilizing published PK data after intravenous administration. Assuming that the human body is a linear systemic disposition kinetics. the plasma concentration in blood $C_p(T_j)$ can be approximated by the following equation, as described by Yu et al[6].

$$C_p(T_j) = \sum_{i=1}^{j} R(T_i) \sum_{k=1}^{m} \{\frac{c_k}{\lambda_k}[e^{-\lambda^k(T_j-T_i)} - e^{-\lambda^k(T_j-T_i-1)}]\} \quad (1)$$

The cumulative amount of drug absorbed, R_{abs}(T) is given by:

$$R(T_j) = \frac{C_p(T_j) - \sum_{i=1}^{j-1} R(T_i)\{\sum_{k=1}^{m} \frac{c_k}{\lambda_k}[e^{-\lambda^k(T_j-T_i)} - e^{-\lambda^k(T_j-T_{i-1})}]\}}{\sum_{k=1}^{m} \frac{c_k}{\lambda_k}(1-e^{-\lambda^k(T_j-T_{j-1})})} \quad (2)$$

Use an equal step length numerical deconvolution algorithm: $a = T_i - T_{i-1}$ for all i. (1)- (2) can be written as:

$$C_p(ja) = \sum_{i=1}^{j} R(ia) \sum_{k=1}^{m} \{\frac{c_k}{\lambda_k}[e^{-\lambda^k(ja-ia)} - e^{-\lambda^k(ja-ia+a)}]\} \quad (3)$$

The cumulative amount of drug absorbed, R_{abs}(a) is given by:

$$R(ja) = \frac{C_p(ja) - \sum_{i=1}^{j-1} R(ia)\{\sum_{k=1}^{m} \frac{c_k}{\lambda_k}[e^{-\lambda^k(ja-ia)} - e^{-\lambda^k(ja-ia+a)}]\}}{\sum_{k=1}^{m} \frac{c_k}{\lambda_k}(1-e^{-\lambda^k a})} \quad (4)$$

Where $C_p(T_j)$ is plasma concentration in blood; $R(T_i)$ is drug absorption rate; c^k and λ^k can be obtained by nonlinear least-squares fitting of normalized unit-dose impulse response experimental data fitting of normalized unit-dose impulse response experimental data.

2.4 PK Simulation Approach

One semi-mechanical model is shown in Figure1. Data from in vitro experiments was used as input parameters for the semi-mechanical model, the output of model was used to predict the plasma concentration-time distribution of polymyxin B [7]. Clinically relevant NGI experiment results were used to generate in vitro input parameters of PK simulation.

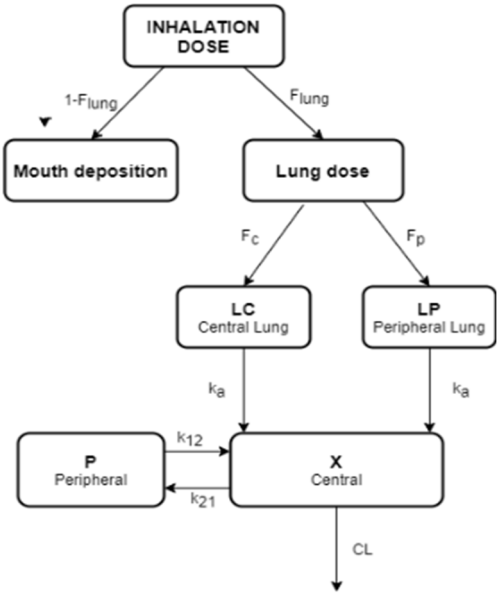

Figure 1: Compartmental model for predicting plasma concentrations after administration of inhaled drug products. Flung: fraction of the emitted dose that is deposited in the lung, (1-Flung): fraction of the emitted dose that is deposited in the oropharynx; FC fraction of the lung dose that is deposited in central regions of the lung; FP fraction of the lung dose that is deposited in peripheral regions of the lung; ka drug absorption from central into the systemic circulation; k12 and k21 drug distribution between central and peripheral body compartments; CL drug elimination from the systemic circulation[7].

3. Result and discussion

3.1 Particle Size

The atomized water mesh nebulizer showed a relatively wide particle size distribution with an X50 of 7.73μm. Optical particle size of atomized polymyxin B solution at the same flow rate is significantly smaller than that of water probably due to the better surface activity of ionic

particles compared to water. Under same air flow rates (15L/min), atomized water and polymyxin solution have little effect on optical particle size D10 and D50, and D90 increases with the increase of the flow rate, with a variation of about 10%.

Table 1: Particle Size of the nebulized polymyxin Measured by Symaptec.

	D10 (μm)	D50 (μm)	D90 (μm)
Water	2.56±0.2	7.73±0.2	14.41±0.3
Polymyxin B solution	1.47±0.1	3.61±0.2	6.74±0.3

3.2 Aerodynamic Performance

In general, particles with aerodynamic diameters of 0.5 and 5μm can reach the lungs. Proper aerodynamic behavior was required to obtain particles suitable for inhalation therapy. The aerodynamic particle size distribution was characterized by NGI. Evaporation of water occurs after a short time of inactivation of a drug solution after atomization. Difficulties in particle collection was increased.

The FPF total reached above 66% and demonstrated high aerodynamic efficiency. For the polymyxin formulation, aerosol deposition behavior is shown in Figure 2. Approximately 3.62% of drug particles was retained in the mesh nebulizer after aerosolisation. Approximately 2.8% of drug particles deposited on filter (<0.98μm) showed a small proportion of ultra-fine particles present in the aerosol. Because inertia impact and sedimentation can be ignored, ultrafine particles can be exhaled (<0.5μm)[8]. However, deep and slow inhalation or breath-holding will help its deposition in the lungs.

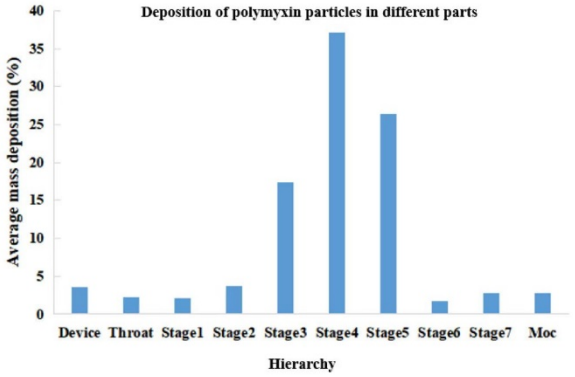

Figure 2: Aerosol deposition behavior of the polymyxin B solution on each stage of NGI using mesh nebulizer.

3.3 Absorption Rate of Polymyxin

Absorption-time data generated under 3 similar subjects are shown in Tables 2. The absorption rate of the drug reached the maximum at about 1h, which is consistent with the trend of plasma concentration of polymyxin clinical data. For the analysis of real pharmacokinetic data, the equal-step numerical deconvolution method is suitable. When a function can reasonably represent the drug input rate, the nonlinear regression numerical deconvolution method and the smooth fixed-step numerical deconvolution method will improve the numerical accuracy and numerical stability[9].

Table 2: Simulated exact absorption-time data for three cases.

Time(h)	Case 1	Case 2	Case 3
1	43.89	56.83	93.15
2	10.18	17.33	47.93
3	8.67	6.29	25.76
4	3.56	15.33	22.41
5	0.89	17.28	19.61
6	2.03	14.38	21.46
7	1.97	11.29	18.45
8	1.68	13.17	20.85
9	1.45	11.32	20.72
10	2.00	7.75	16.64

3.3 Pulmonary PK simulation

The Multiple-Path Particle Dosimetry Model (MPPD v 3.04, https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304) was used to estimate the central to peripheral (c/p) lung deposition fractions of inhaled particles[7]. Matlab dsolve module was used to solve the concentration - time differential equation of the model and the input parameters[10] are shown in Table 3.

Table 3: Parameters related to semi-mechanical simulation.

	CL	Vc	k12	k21
Unit	Kg/h	kg	h^{-1}	h^{-1}
Input	3.54	3.06	1.78	0.09

In this study, the drug absorption rate of intravenous polymyxin derived by deconvolution method was used as the input of model to explore. Figure 3[11] show simulated plasma concentration compared with plasma concentration of aerosol CMS patients. The absorption of the drug reached its highest rate 1 hour after inhalation and then gradually weakened with time, which was consistent with the trend of blood concentration after intravenous injection. Blood drug concentration curves obtained from simulation were relatively similar to those of CMS. An important input parameter in this semi-mechanical model is the absorption rate of the drug. However the absorption rate through the lungs of aerosolized drug is difficult to evaluate experimentally, and PK data for aerosolized polymyxin B are lacking clinically. It is also important to note that CMS are not pharmaceutically active in vivo and require conversion to colistin E for efficacy. The plasm concentration of subjects is higher than simulated result may because CMS is not absorbed at 2-6 hours, but is slowly converted to the active drug CBA.

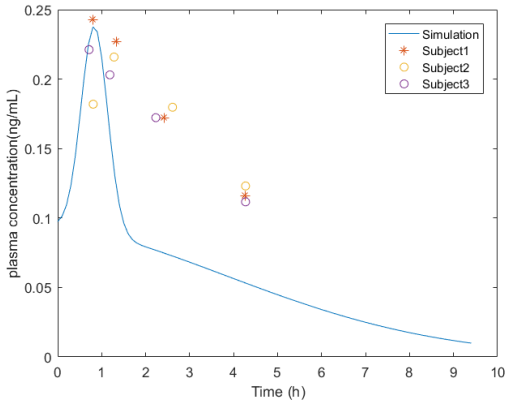

Figure 3: Simulated concentration-time profile of aerosol polymyxin B to 3 subjects.

4. Conclusions

Overall, given the highly variable nature of studying lung-targeted pharmacokinetics, the plasma concentration profile of polymyxin B aerosol inhalation was predicted by using an isometric inverse fold product method to estimate the drug absorption rate. It should be re-emphasized that this method assumes the same absorption rate of nebulized drug particles in the lungs as intravenous injection and uses a two-compartment semi-mechanical model for simulations that cannot explain the mechanism in depth. However, the blood drug concentration profiles obtained were relatively similar to those of CMS. The absorption rate obtained by deconvolution algorithm can reasonably predict the pharmacokinetics of aerosolized polymyxin B.

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