Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis

Jian Li¹†, Kingsley Coulthard¹²*, Robert Milne¹, Roger L. Nation¹†, Steven Conway³, Daniel Peckham³, Christine Etherington³ and John Turnidge⁴

¹Centre for Pharmaceutical Research, School of Pharmaceutical, Molecular and Biomedical Sciences, University of South Australia, Adelaide; Departments of ²Pharmacy, and ⁴Microbiology and Infectious Diseases, Women’s and Children’s Hospital, North Adelaide, SA 5006, Australia; ³Regional Adult Cystic Fibrosis Unit, Seacroft Hospital, Leeds, UK

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Objectives: To define the steady-state pharmacokinetics of colistin methanesulphonate and colistin in patients with cystic fibrosis (CF) following intravenous administration of the former.

Materials and methods: The study was conducted in 12 patients with CF following intravenous administration of colistin methanesulphonate (1.63–3.11 mg/kg) every 8 h for at least 2 days. On the day of study, four blood samples were collected from each patient at 60, 120, 240 and 360 min after the end of the infusion. Concentrations of colistin methanesulphonate and colistin in plasma were measured separately by HPLC.

Results: At steady-state, colistin methanesulphonate had a mean (± S.D.) total body clearance, volume of distribution and half-life of 2.01 ± 0.46 mL/min per kg, 340 ± 95 mL/kg and 124 ± 52 min, respectively. Colistin had a significantly longer mean half-life of 251 ± 79 min (P < 0.001). With the regimen used, colistin methanesulphonate was well tolerated. This is the first report on the pharmacokinetics of colistin methanesulphonate in CF patients determined using concentrations of colistin methanesulphonate and colistin in plasma.

Conclusions: Based on the in vitro pharmacodynamics against Pseudomonas aeruginosa previously published by our group and these pharmacokinetic findings, dose escalating trials may be warranted to maximize efficacy.

Keywords: colistin, HPLC, pharmacodynamics, Pseudomonas

Introduction

The increasing prevalence of infections caused by multidrug-resistant Pseudomonas aeruginosa is a major clinical problem,¹² especially in patients with burns, neutropenia and cystic fibrosis (CF).³ CF is one of the most common genetic diseases in western countries.⁴ More than 90% of patients with CF die of respiratory failure, in particular as a result of P. aeruginosa infections and the associated host inflammatory responses.⁵ Colistin, also known as polymyxin E, was the first antibiotic with notable in vitro activity against P. aeruginosa and was commercially released in 1959.⁶ Subsequently, colistin was relegated to a second line antibiotic because of its potential systemic toxicity, including neurotoxicity and nephrotoxicity, and the availability of less toxic anti-pseudomonal antibiotics.⁷ However, the significant resistance of P. aeruginosa to the commonly used antibiotics and the lack of truly novel classes of anti-pseudomonal agents in development have generated renewed interest in this ‘old’ antibiotic.⁷–¹¹ Colistin has rapid bactericidal activity with a detergent-like mechanism,¹² and fortunately resistance is unusual and develops slowly.¹⁰

Colistin is a multi-component polypeptide antibiotic with colistin A (polymyxin E₁) and colistin B (polymyxin E₂) being the two major components.¹³,¹⁴ Two different forms of colistin are available commercially, colistin sulphate for oral and topical use, and sodium colistin methanesulphonate for parenteral and aerosol use. Sodium colistin methanesulphonate is produced by the reaction of colistin with formaldehyde and sodium bisulphite.¹⁵,¹⁶ Compared with colistin, the in vitro antibacterial potency of colistin methanesulphonate

†Present address. Victorian College of Pharmacy, Monash University, Parkville, Victoria 3052, Australia.
*Corresponding author. Tel: +61-8-8161-7350; Fax: +61-8-8161-6049; E-mail: coulthardk@wch.sa.gov.au

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is considerably reduced, as are the toxic and undesirable side effects. Colistin methanesulphonate has the potential to hydrolyse in aqueous solution and form an extremely complex mixture of partial sulphomethyl derivatives, plus colistin, which has increased antibacterial activity.

Recent reports have assessed the effectiveness, safety and tolerability of intravenously administered colistin methanesulphonate and concluded that it is an efficacious treatment for P. aeruginosa infections associated with pulmonary exacerbations in CF patients. Unfortunately, the pharmacokinetics of colistin methanesulphonate in CF patients have not been comprehensively studied despite its commercial availability for over 40 years. Most available data on its pharmacokinetics in humans were obtained with concentrations of drug in plasma and urine measured by microbiological assays. However, microbiological assays are unable to quantify colistin methanesulphonate and colistin separately. Recently, Reed et al. described the pharmacokinetics of colistin methanesulphonate after iv administration in CF patients, using high-performance liquid chromatography (HPLC) to measure the concentrations of drug in plasma and urine following derivatization with dansyl chloride. However, previous studies in our laboratory have shown that colistin methanesulphonate hydrolyses to colistin via its partial derivatives when stored in plasma at 37°C. Substantial in vitro hydrolysis of colistin methanesulphonate to colistin may have occurred while heating for 2 h at 54 or 57°C during preparation of the samples for HPLC analysis, and hence it is not clear which form, colistin methanesulphonate, colistin or both, was quantified by their HPLC method. Therefore, the preceding pharmacokinetic parameters estimated for colistin methanesulphonate are best regarded as average values for the fully and partially sulphomethylated derivatives plus colistin. In addition, the HPLC method used in that previous study had a relatively high limit of quantification (5 mg/L with 1 mL plasma).

Two sensitive HPLC methods have been developed in our laboratory for colistin and colistin methanesulphonate. The aim of this study was to examine the pharmacokinetics of colistin methanesulphonate and colistin at steady-state in CF patients during treatment with iv infusions of colistin methanesulphonate.

Materials and methods

Chemicals and reagents

Sodium colistin methanesulphonate (Colo-Mycin) was supplied from Pharmax (Batch Number: 11860, Kent, UK; 1 mg contained approximately 12 740 units). Colistin sulphate and 9-fluorenylmethyl chloroformate (FMOC-Cl) were purchased from Sigma (St Louis, MO, USA), and netilmicin sulphate from Schering-Plough (Madison, NJ, USA). All other chemicals were from suppliers described previously.

Patients and ethics

Twelve CF patients (six males and six females) entered this study, all with acute pulmonary exacerbation caused by infections with P. aeruginosa. The study protocol was approved by the Clinical Research Ethics Committee at St James’ and Seacroft University Hospital, Leeds, UK, and informed consent was obtained from all patients before entry. All patients had been administered colistin methanesulphonate on previous occasions. Clinical and demographic data for the 12 study subjects are presented in Table 1. In total, there were 33 colony types of P. aeruginosa isolated from the patients; 44% were resistant to piperacillin, 30% to tobramycin, 25% to ciprofloxacin, 25% to cefazidime, 47% to amikacin, 31% to aztreonam, 25% to meropenem and 3% to colistin, as defined by Stokes comparative disc diffusion method. No patient had renal impairment or a history of hypersensitivity or neurological toxicity to colistin.

Treatment

According to the Unit’s guidelines, patients weighing more than 50 kg received 2 million units of colistin methanesulphonate (160 mg, dissolved in 50 mL of sterile saline) whereas those less than 50 kg were administered 1 million units (80 mg, dissolved in 50 mL of sterile saline) intravenously every 8 h. The dosing solution was stored at 4°C and discarded if not used within 3 days. Colistin methanesulphonate was given as a 50 mL infusion over 15–60 min. To monitor the potential neurotoxicity related to treatment with colistin methanesulphonate, subjects were repeatedly questioned throughout the study and requested to report any adverse effects; any such adverse effects were to be categorized as possible, probable or definite in terms of their causation in relation to the administration of colistin methanesulphonate. Potential nephrotoxicity was assessed by determination of serum creatinine on day 0, 7 and 14 of therapy. After at least 2 days of therapy had elapsed, blood samples (4 mL) were obtained with 4 mL heparinized Vacuette containers (Greiner Labortechnik, Austria) at 60, 120, 240 and 360 min (sampling time varied slightly in some patients) from the end of the infusion. The samples were centrifuged (1000g, 10 min) immediately at 4°C and plasma stored at −60°C until analysis.

Determination of colistin methanesulphonate and colistin in plasma

The concentrations of colistin methanesulphonate and colistin in plasma were measured by two sensitive HPLC methods developed in our laboratory with some modifications. For the assay of colistin, briefly, plasma (250 μL) was mixed with netilmicin (internal standard), proteins precipitated and the supernatant transferred to a solid-phase extraction (SPE) C18 cartridge (Sep-Pak, Waters, Milford, MA, USA), in which fluorescent derivatives of FMOC were formed. Elution of the derivatives was followed by reversed-phase HPLC with detection by fluorescence. Modifications from the previously described method included 10 μL netilmicin (2.5 mg/L), a mobile phase of acetonitrile–tetrahydrofuran–water (50:30:20, v/v) and a shortened run time of 18 min. Calibration standards were prepared in drug-free human plasma with concentrations of colistin sulphate ranging from 0.08 to 3.2 mg/L. The accuracy and reproducibility were 0.23±0.008 and 2.42±0.04 mg/L for the independently prepared quality control samples containing colistin sulphate at 0.24 and 2.4 mg/L, respectively (n = 3). The limit of quantification was 0.08 mg/L. The concentrations of colistin were calculated by multiplying the obtained concentrations of colistin sulphate by 1163/1403, where 1163 is the average molecular weight of colistin A and colistin B, and 1403 is the average molecular weight of the corresponding sulphates. The total colistin species (colistin methanesulphonate, plus partially sulphomethylated derivatives plus free colistin) in plasma were assayed by HPLC. Calibration standards containing colistin methanesulphonate were freshly prepared in drug-free human plasma over the range from 0.20 to 32 mg/L. The accuracy and reproducibility were 0.81±0.04 and 23.8±0.7 mg/L for the independently prepared quality control samples containing colistin methanesulphonate at 0.80 and 24 mg/L, respectively (n = 3). The limit of quantification was 0.20 mg/L. The concentration of ‘colistin methanesulphonate’ (colistin methanesulphonate plus partially sulphomethylated derivatives) was the value calculated above (as total colistin species) minus the concentration of colistin in the same sample, after correcting for differences in the average molecular weights of colistin (1163, from the molecular weights for colistin A and colistin B of 1170 and 1156, respectively) and sodium colistin methanesulphonate (1743, from the molecular weights for sodium colistin A methane-
Pharmacokinetics of colistin methanesulphonate in CF patients

Table 1. Clinical and demographic data of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Body weight (kg)</th>
<th>Dose (mg/kg per dose)</th>
<th>Infusion duration (min)</th>
<th>Serum creatinine (µM)</th>
<th>Sampling day</th>
<th>Antibiotics co-administered</th>
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<tr>
<td>1</td>
<td>18</td>
<td>M</td>
<td>60</td>
<td>2.62</td>
<td>30</td>
<td>87</td>
<td>3</td>
<td>meropenem (iv), oral flucloxacillin, aztreonam (iv), oral flucloxacillin and fusidic acid ceftazidime (iv), oral flucloxacillin</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>F</td>
<td>45</td>
<td>1.74</td>
<td>30</td>
<td>60</td>
<td>17</td>
<td>ceftazidime (iv)</td>
</tr>
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<td>3</td>
<td>21</td>
<td>F</td>
<td>61</td>
<td>2.58</td>
<td>30</td>
<td>53</td>
<td>7</td>
<td>ceftazidime (iv)</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>68</td>
<td>2.32</td>
<td>10</td>
<td>77</td>
<td>9</td>
<td>tazocin (iv) (piperacillin and tazobactam), oral flucloxacillin, inhaled tobramycin</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>F</td>
<td>48</td>
<td>1.63</td>
<td>15</td>
<td>NA</td>
<td>3</td>
<td>meropenem (iv), oral flucloxacillin aztreonam (iv), oral flucloxacillin ceftazidime (iv), oral flucloxacillin ceftazidime (iv)</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>52</td>
<td>3.02</td>
<td>30</td>
<td>50</td>
<td>7</td>
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<td>7</td>
<td>22</td>
<td>F</td>
<td>39</td>
<td>2.01</td>
<td>30</td>
<td>53</td>
<td>6</td>
<td>meropenem (iv), oral flucloxacillin aztreonam (iv), oral flucloxacillin meropenem (iv), oral flucloxacillin</td>
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<tr>
<td>8</td>
<td>19</td>
<td>M</td>
<td>61</td>
<td>2.58</td>
<td>15</td>
<td>64</td>
<td>11</td>
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<td>9</td>
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<td>66</td>
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<td>M</td>
<td>64</td>
<td>2.44</td>
<td>20</td>
<td>79</td>
<td>6</td>
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<tr>
<td>11</td>
<td>19</td>
<td>M</td>
<td>60</td>
<td>2.64</td>
<td>20</td>
<td>53</td>
<td>6</td>
<td>meropenem (iv), oral flucloxacillin and fusidic acid, inhaled tobramycin</td>
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<tr>
<td>12</td>
<td>18</td>
<td>M</td>
<td>51</td>
<td>3.11</td>
<td>30</td>
<td>96</td>
<td>4</td>
<td>meropenem (iv), oral flucloxacillin and fusidic acid, inhaled tobramycin</td>
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<tr>
<td>Mean</td>
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<td></td>
<td></td>
<td>66</td>
<td>6.8</td>
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<td>S.D.</td>
<td>6.9</td>
<td>9</td>
<td>0.45</td>
<td></td>
<td></td>
<td>16</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

Note: NA, not available.

a Serum concentration of creatinine on the day of admission. The normal range of serum creatinine concentrations is 53–84 µM for females and 71–106 µM for males.
b The day of sampling after the first dose.

None of the other antibiotics administered to some patients (Table 1) interfered in the analysis of colistin methanesulphonate and colistin in plasma.

Pharmacokinetic analysis

It was assumed that the concentrations of colistin methanesulphonate and colistin in plasma were at steady-state. Since comprehensive blood sampling was not possible in the current study, for the purpose of calculating pharmacokinetic parameters (vide infra), it was assumed that the concentrations of colistin methanesulphonate and colistin declined in a monoexponential manner after completion of the infusion. Therefore, the \( k_e \) (disposition rate constant) was calculated by linear least-squares regression analysis without weighting (WinNonlin, V3.0, Pharsight Corp., Cary, NC, USA) using the four log-transformed plasma concentration versus time points for colistin methanesulphonate and colistin. The area under the concentration versus time curve during a dosage interval at steady-state) was calculated by extrapolation back to when the infusion was ceased and forward to 8 h, respectively. The plasma concentration immediately preceding the start of the infusion was presumed equal to \( C_{\text{max}} \). Therefore, \( AUC_t = \frac{D}{C_{\text{max}}} \) where \( D \) is the dose of colistin methanesulphonate.

Statistical analysis

Differences between the values of \( t_{1/2} \) for colistin methanesulphonate and colistin were evaluated with a paired \( t \)-test. A \( P \) value less than 0.05 was considered significant. The 95% confidence interval for the difference was determined.

Stability of colistin methanesulphonate in saline at 4°C

A solution of colistin methanesulphonate (10 mg/mL) was prepared in saline and kept at 4°C pending analysis of the concentration of colistin by HPLC.24

Results

The infusion solution of colistin methanesulphonate contained only a very small amount of colistin since the stability study indicated that less than 0.06% of colistin methanesulphonate stored in saline for 72 h at 4°C was present in the form of colistin. Except for patient 9, who experienced itching of the scalp, eyebrows and face when the dose was given in a 30 min infusion on day two of treatment with colistin methanesulphonate, no adverse events were reported during the study. The plasma concentration versus time profiles for colistin methanesulphonate and colistin for all patients are shown in Figure.
The pharmacokinetic parameters of colistin methanesulphonate and colistin are presented in Table 2. The half-life of colistin methanesulphonate (124 ± 52 min) was significantly shorter than that of colistin (251 ± 79 min) \( (P < 0.001) \); the mean difference in half-life between colistin and colistin methanesulphonate was 127 min (95% CI 81, 174).

**Discussion**

As also observed in the current study, clinical isolates of *P. aeruginosa* have demonstrated high resistance to the commonly used antipseudomonal antibiotics.\(^\text{26}\) Fortunately, colistin methanesulphonate maintains antibacterial activity with resistance being rare,\(^\text{7,10,19}\) as was also observed in the isolates obtained in this study. Even though several HPLC methods have been reported for measuring colistin levels in human serum,\(^\text{27}\) plasma,\(^\text{24}\) and in bovine tissues,\(^\text{28}\) none of these methods was applied to colistin methanesulphonate. The concentrations of drug in plasma and urine reported in all previous studies by microbiological assays or HPLC are most likely values for a mixture of colistin methanesulphonate and colistin. Therefore the published pharmacokinetics of colistin methanesulphonate based on these data should also be regarded as values for a mixture. Since colistin has higher overall bactericidal and post-antibiotic activities against *P. aeruginosa* than colistin methanesulphonate,\(^\text{18}\) it will be of greater value to obtain the concentrations of each form separately when investigating their in vivo pharmacodynamics. This study was designed to measure separately the plasma concentrations of both forms after the iv administration of

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**Figure 1.** Concentrations of colistin methanesulphonate (a) and colistin (b) in plasma from the CF patients.
colistin methanesulphonate using two novel HPLC methods developed in our laboratory.24,25 This has allowed a more detailed description of the pharmacokinetics of colistin methanesulphonate and the colistin formed in humans, than has hitherto been possible.

The half-life of colistin methanesulphonate in the 12 patients ranged from 82 to 268 min, and that of colistin was from 139 to 385 min (Table 2). Therefore, plasma concentrations could be assumed to be at steady-state in this study when the samples were collected more than 2 days after the first dose (Table 1). Clinical and ethical considerations precluded the collection of more than four blood samples within the dosing interval; this would have allowed a more accurate determination of AUC\textsubscript{τ}.\textsuperscript{10} The decline in concentrations of colistin methanesulphonate and colistin was assumed to be monoexponential. However, it is possible that this assumption, and extrapolation for calculated concentrations at the beginning and end of the infusion, provided an underestimate of the true AUC\textsubscript{τ}. This would lead to the overestimation of the CL and V.

In the current study, colistin methanesulphonate had a CL, V and half-life of 2.01 ± 0.46 mL/min per kg, 340 ± 95 mL/kg and 124 ± 52 min, respectively. Comparison of these values with those published previously is difficult since very few early studies in humans provided pharmacokinetic data and most reports focused only on the plasma and urine concentrations of colistin methanesulphonate measured by microbiological assays.\textsuperscript{8,19,20} The values for CL and V of colistin methanesulphonate in the current study were higher than the values of 0.35 ± 0.09 mL/min per kg and 0.09 ± 0.02 L/kg reported by Reed et al. using non-compartmental analysis.\textsuperscript{8} The patients in the current study were younger (age 21.7 ± 6.9) than those (29.4 ± 10.3) reported by Reed et al.,\textsuperscript{8} but they had similar body weights (56 ± 9 kg versus 50 ± 8.1 kg). We have shown that concentrations of colistin after a dose of colistin methanesulphonate are comparable between these two species.\textsuperscript{24,25}

Table 2. Pharmacokinetic parameters of colistin methanesulphonate and colistin in CF patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>AUC\textsubscript{τ} (mg min/L)</th>
<th>CL (mL/min per kg)</th>
<th>V (mL/kg)</th>
<th>t\textsubscript{1/2} (min)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>157</td>
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<td>Mean</td>
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<td>404</td>
<td>124</td>
<td>251</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.46</td>
<td>95</td>
<td>52</td>
<td>79</td>
</tr>
</tbody>
</table>

Colistin had a half-life significantly longer than that of colistin methanesulphonate. This indicated that elimination of colistin, rather than its formation, is the rate-limiting factor in its disposition in the body. The half-lives in humans are longer than those observed in rats (23.6 ± 3.9 min for colistin methanesulphonate and 55.7 ± 19.3 min for colistin) after an iv bolus of colistin methanesulphonate (unpublished results). It is noteworthy that the relativity in values is comparable between these two species.

Koch-Weser et al.\textsuperscript{29} reported on the common occurrence of severe adverse effects in humans after intramuscular injection of colistin methanesulphonate (4.0–5.4 mg/kg per day). In the current study, no adverse events occurred, except in patient 9 who experienced itching of the scalp, eyebrows and face; the side effects were subsequently overcome in this patient by slower infusion (1 h). The doses administered in this study (approximately 7.26 mg/kg per day), although higher than those administered by Koch-Weser et al.,\textsuperscript{29} were well tolerated. As a result of the complexity of the patients’ underlying illnesses, Koch-Weser et al. may have concluded erroneously that colistin was the primary cause of the severe adverse effects.\textsuperscript{29} It is also possible that the solution of colistin methanesulphonate administered by Koch-Weser et al.\textsuperscript{29} contained a substantial proportion of colistin. Overall, the good tolerability observed for iv administration of colistin methanesulphonate in this study was consistent with recent reports.\textsuperscript{8,19,20,30}

The calculated C\textsubscript{max} and C\textsubscript{min} of colistin methanesulphonate, estimated by extrapolation to the end of the infusion and the end of the dosing interval, respectively, ranged from 3.6 to 13.2 mg/L and from 0.18 to 2.0 mg/L, respectively. For colistin, the ranges of calculated C\textsubscript{max} and C\textsubscript{min} were 1.2–3.1 and 0.14–1.3 mg/L, respectively (data not shown). The C\textsubscript{max} of colistin methanesulphonate and colistin, even without consideration of protein binding, were in the same range as the MICs observed previously for susceptible isolates of P. aeruginosa from CF patients (1–4 mg/L for colistin and 4–16 mg/L for colistin methanesulphonate).\textsuperscript{18} The concentrations of colistin methanesulphonate in plasma were substantially less than the 16 ×
MIC (64–256 mg/L) required for complete in vitro killing within 24 h and for a significant post-antibiotic effect. Similarly, the concentrations of colistin were approximately 0.5 × MIC (0.5–2 mg/L), a concentration range at which P. aeruginosa could not be eradicated in 24 h and also where there was no significant post-antibiotic effect. Therefore, doses higher than those in the current study might enhance the efficacy of colistin methanesulphonate. Undoubtedly, MICs of colistin and colistin methanesulphonate against different P. aeruginosa isolates may extend over a broad range. Therefore, care is needed in comparing the MICs with the concentrations for both agents in plasma after administration of colistin methanesulphonate. Obviously, there is also the possibility for an additive antibacterial effect when these two compounds are present simultaneously in plasma.

Conclusions

This is the first report on the pharmacokinetics of colistin methanesulphonate determined using concentrations of colistin methanesulphonate and colistin measured separately in plasma by two sensitive HPLC methods. Since colistin methanesulphonate and colistin have different pharmacokinetics and in vitro pharmacodynamics, the results will assist in refining the clinical use. Taken together with our earlier in vitro pharmacodynamic data, our results indicate that clinical trials using higher doses of colistin methanesulphonate, possibly administered less frequently, are necessary. The pharmacokinetic data from this study could provide initial guidance as to the appropriate doses to utilize in such a trial. Furthermore, as CF patients usually have high drug clearance, the current results cannot be extrapolated, without further study, to other populations with multidrug-resistant Gram-negative bacterial infections.

Acknowledgements

We are grateful to Mr Jason Valentine for his assistance with the shipping of the samples.

References