Pharmacokinetics of high-dose extended-infusion meropenem during pulmonary exacerbation in adult cystic fibrosis patients: a case series

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SUMMARY

This case series explored the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of meropenem (MEM) in adult cystic fibrosis (CF) patients hospitalized for a pulmonary exacerbation. From January 2015 to June 2016, all adult patients with cystic fibrosis (CF) and chronic pulmonary infection due to meropenem (MEM)-susceptible/intermediate *Pseudomonas aeruginosa* who received at least 48 h of MEM as an extended 3-hour infusion for treating a pulmonary exacerbation were enrolled. MEM plasma concentrations were determined by high-performance liquid chromatography. Six adult CF patients with a median age of 47 years were included in the study. MEM showed a high Vd (mean 45.98 L, standard deviation [SD] ±34.45). A minimal PK/PD target of 40% T > minimum inhibitory concentration (MIC) with respect to the MEM MIC of *P. aeruginosa* strains isolated from sputum during exacerbation was achieved in 5/6 patients (83%). MEM failed to achieve this target only in one patient, whose strain showed the highest MEM MIC in our cohort (8 mg/L). In all patients, MEM was well tolerated, and no adverse events were reported. In conclusion, high-dose, extended-infusion MEM during pulmonary exacerbation showed a high Vd in six adult CF patients with high median age, and was well tolerated.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive multi-organ disease (Cystic Fibrosis Foundation, 2015). Although its clinical course varies markedly according to genetic, environmental, and microbiological factors, it is usually dominated by chronic pulmonary infection and bronchiectasis, with recurrent acute exacerbations requiring intravenous antibiotics (Flume 2009; Al-Aloul 2004; Cystic Fibrosis Foundation, 2015). In recent decades, advances in modern medicine have led to a substantial increase in the life expectancy of CF patients, and the reported median survival time is now longer than 40 years in several countries (Cystic Fibrosis Canada, 2013; Cystic Fibrosis Foundation, 2015). Since both CF pulmonary exacerbation rates and the prevalence of chronic pulmonary infection caused by cephalosporin-resistant *Pseudomonas aeruginosa* increase with age (Cystic Fibrosis Foundation, 2015; Mustafa *et al.,* 2016), many more adult CF patients than before are now given intravenous meropenem (MEM), a carbapenem exerting anti-pseudomonal activity (Craig *et al.,* 1997), for treating recurrent episodes of pulmonary exacerbation. Since MEM is one of the last-resort agents in CF patients with chronic pulmonary infection due to *P. aeruginosa*, its use should be necessarily optimized from a pharmacokinetic/pharmacodynamic (PK/PD) perspective, both to improve activity and to reduce the selection of carbapenem-resistant strains. The PK/PD characteristics of MEM have recently been investigated in CF children with pulmonary exacerbation. The drug showed a good PK/PD profile when administered as a 3-hour extended infusion, and was well tolerated (Pettit *et al.,* 2016).

In contrast, although previous PK/PD data of MEM in adult CF patients have been published, PK/PD information in adult CF patients during pulmonary exacerbation remains scant (Kuti *et al.,* 2004a; Bulik *et al.,* 2010; Kuti *et al.,* 2004b). The primary objective of this study was to describe the PK/PD characteristics of MEM in adult CF patients hospitalized for a pulmonary exacerbation in a large teaching hospital in northern Italy.

MATERIALS AND METHODS

From January 2015 to June 2016, we conducted a prospective study at the University of Genoa IRCCS AOU San

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Martino-IST, a 1,300-bed teaching hospital in Genoa, Italy. The study was approved by the local ethics committee and all enrolled patients signed an informed consent form to participate in the study. During the study period, all adult patients with cystic fibrosis (CF) and chronic pulmonary infection due to meropenem (MEM)-susceptible/intermediate *P. aeruginosa* who received at least 48 h of MEM as an extended 3-hour infusion for treating a pulmonary exacerbation were included in the study. Exclusion criteria were an estimated creatinine clearance (CrCl) <10 mL/min according to Cockcroft-Gault formula (Cockcroft *et al.*, 1976), renal replacement therapy, pregnancy, and a history of hypersensitivity to beta-lactams. The primary study endpoints were plasma PK parameters of MEM in enrolled patients. Secondary endpoints were achievement of plasma PK/PD targets and tolerability.

Antibiotic therapy and definitions

The use of MEM and of any possible other concomitant antibiotic was decided in every single case by the physician in charge, according to his/her clinical judgment and independent of the study protocol. In line with the standard practice in our center, MEM was administered as an extended 3-hour infusion of 2 g every 8 hours.

Chronic pulmonary infection was defined as the persistent growth of *P. aeruginosa* in sputum cultures collected for at least 6 consecutive months, reflecting standard definitions (Lee, *et al.*, 2003). The presence of pulmonary exacerbation was defined according to Fuch's criteria (Fuchs *et al.*, 1994).

Microbiology

The Vitek 2 AES automated system (bioMérieux, Marcy l'Etoile, France) was used for identification of *P. aeruginosa* isolates defining chronic pulmonary infection. In addition, quantitative cultures were performed by means of serial dilution of 500 µl of sputum in 4.5 ml of 0.85% NaCl. Diluted samples were inoculated into standard MacConkey, blood, mannitol salt and chocolate agar plates and incubated at 35°C in an aerobic atmosphere, according to standard procedures. The Vitek 2 AES automated system was also used for susceptibility testing. Meropenem MIC was confirmed by the e-test (bioMérieux, Marcy l'Etoile, France) method. Susceptibility results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (Breakpoint for interpretation of MIC and zone diameters. Version 7.1, 2017; www.eucast.org).

MEM concentration determination

MEM plasma concentrations were determined for each patient after 48 h of drug infusions. Blood samples were collected as follows: immediately after the end of infusion, and 1, 3, and 5 hours afterwards. MEM plasma concentrations were evaluated by validated high-performance liquid chromatography assay as described elsewhere (Legrand *et al.*, 2008; Del Bono *et al.*, 2017). The calibration curves of peak areas vs. meropenem concentrations were linear from 0.5 up to 50 mg/L, giving a correlation coefficient of r2=0.999. Two replicates of each quality control plasma sample (QC 1, 5, 25 mg/L) and the Lower Limit of Quantification (LLOQ 0.5 mg/L) were analyzed on 3 different days and subjected to within and between run analysis. The results, as far as precision and accuracy are concerned, are derived from the measured concentrations

of the validation samples, and were acceptable according to The International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Q2(R1) and Washington criteria (International Conference on Harmonization, 1996; Shah *et al.*, 1992).

MEM pharmacokinetic analysis

MEM pharmacokinetic parameters were determined by non-compartmental methods using 2.1 Phoenix WinNonlin Professional Edition (Pharsight International France Sàrl). The main parameters calculated for each patient were maximum plasma concentration (C_{max}), area under the plasma concentration-time curve, from 0 to 8 hours postdose (AUC_{last}) and from 0 hours extrapolated to infinity, based on the last observed concentration ($AUC_{0-\infty-obs}$), elimination rate constant (Ke), mean residence time (MRT), constant rate of infusion (R_0), Clearance (Cl) calculated as Dose/ AUC_{0-8h}, Volume of distribution (V_d) calculated as Cl*MRT, and terminal half-life ($T_{1/2}$). The achievement of PK/PD targets was measured in terms of T>MIC, in view of the time-dependent antimicrobial activity of MEM (Craig *et al.*, 1997). T>MIC was defined as the percentage of the dosing interval during which MEM concentrations were higher than the MEM MIC of the last *Pseudomonas aeruginosa* isolated from sputum before/during exacerbation. For each patient/strain pair, T > MIC value was obtained according to the following formula:

$$\% \, T{>}MIC = [[T_{inf}/\ln(C_{3h}/C_{0h})] + (1/K)] \times \ln[C_{3h}/(MIC)] \times (100/\tau) \, (1)$$

where T_{inf} is the length of infusion, C_{3h} is the MEM plasma concentration at the end of infusion ($=C_{max}$), C_{0h} is the MEM plasma concentration at the beginning of the next infusion, K is the rate constant and τ is the time interval between two consecutive doses (Kim *et al.*, 2001). The $\%$ T>MIC was also calculated with respect to hypothetical MEM MICs of 0.25, 0.5, 1, 2, 4, 8, and 16 mg/L, for every patient and with the method described above.

RESULTS

Seven adult CF patients met the inclusion criteria and signed an informed consent form to participate in the study. However, one of them received MEM as a 1-hour infusion, and was therefore excluded from the analyses. Among the 6 remaining patients, the median age was 47 years (interquartile range [IQR] 40-55), and 3/6 were males (50%). Their demographic and clinical characteristics are summarized in *Table 1*, along with information on MEM susceptibility of their last *P. aeruginosa* isolate. All the described *P. aeruginosa* strains were isolated from sputum during the exacerbation episode considered in this study. As shown in the table, MEM MICs of isolates ranged from 0.25 to 8 mg/L. Although 2/6 patients (33%) had also some previous cultures positive for another organism (*Burkholderia cepacia*, and *Achromobacter xylosoxidans*, respectively), none of them were isolated during the episode of pulmonary exacerbation considered in this study. Three patients were treated with MEM monotherapy, and the other three with MEM-including combinations (details are reported in the legend of *Table 1*). All patients recovered their previous forced expiratory volume in 1 s (FEV-1) in good health in the subsequent inter-exacerbation period.

Figure 1 shows the plasma concentration-time profiles of MEM in enrolled patients. *Table 2* summarizes the PK pa-

Table 1 - *Baseline demographic, clinical, and microbiological characteristics of adult CF patients included in the study.*

Patient No.	Age (years)	Gender	CF mutations	Weight (kg)	BMI (kg/m²)	LBM (kg)	Serum creatinine (mg/dl)	CrCl (ml/min)	Diabetes mellitus	Pancreatic insufficiency	Last FEV-1 in good health	MEM MIC of the Pa isolated from sputum during exacerbation (mg/L)	Organisms other-than Pa isolated from previous sputum cultures
1	56	Female	1717-1G->A/ 3849+10kbC->T	65	25	45.1	0.6	107.4	No	No	42%	1	
2	44	Male	F508del/ unknown	54	20	47.6	0.7	102.9	No	Yes	35%	8	
3	50	Female	M1V/ 2789+5G->A	65	23	42.8	0.5	116.2	No	No	40%	1	
4	28	Male	F508del/ G58E	61	21	51.0	0.7	135.6	Yes	Yes	25%	2	*Achromobacter xylosoxidans* (MEM MIC unavailable)
5	39	Male	F508del/ F508del	76	25	60.0	0.8	120.1	No	Yes	35%	0.25	*Burkholderia cepacia* complex (MEM MIC 4 mg/L)
6	68	Female	F508del/ unknown	49	21	37.4	0.7	59.5	No	Yes	45%	2	

CF, cystic fibrosis; BMI, body mass index; LBM, lean body mass; CrCl, creatinine clearance; FEV-1, forced expiratory volume in 1 s; MEM, meropenem, MIC, minimum inhibitory concentration; *Pa, Pseudomonas aeruginosa*. Patients 1, 3, and 6 were treated with MEM monotherapy. Patients 2, 4, and 5 received a 2-drug combination of MEM plus amikacin, MEM plus sulfamethoxazole/trimethoprim, and MEM plus tigecycline, respectively. LBM was estimated from height and weight using the method of James (James, 1976).

rameters of MEM in study patients, along with the PK/PD estimates of the achieved %T > MIC for each patient/isolate pair. As shown, the minimal PK/PD target of 40% T>MIC with respect to the actual MEM MIC of *P. aeruginosa* strains was achieved in 5/6 enrolled patients (83%). MEM failed to achieve this minimal target only in one patient, whose strain showed the highest MEM MIC in our cohort (8 mg/L).

Number and percentages of patients achieving different %T>MIC with respect to hypothetical MICs of 0.25, 0.5, 1, 2, 4, 8, and 16 mg/L are shown in *Table 3*. In line with what is reported above for actual MEM MICs, a minimum PK/

PD target of 40% T>MIC was achievable only for hypothetical MEM MICs <8 mg/L. In all patients, MEM was well tolerated, and no adverse events were reported.

DISCUSSION

The present case series showed a high variability in PK parameters of high-dose, extended-infusion MEM during pulmonary exacerbation, in six adult CF patients with chronic *P. aeruginosa* pulmonary infection. A minimal plasma PK/PD target of 40% T>MIC with respect to respiratory isolates was achieved only for MEM MICs <8 mg/L. To date, the literature on PK parameters of MEM in adult CF patients has provided somewhat conflicting results, although a necessary premise is that published studies are hardly comparable because of different methods and schedules of MEM administration (Kuti *et al.*, 2004a; Christensson *et al.*, 1998; Bui *et al.*, 2001). More in detail, while Christensson *et al.* described a significantly shorter $t_{1/2}$ after infusion of low-dose MEM (15 mg/kg) over 15 minutes in adult CF patients in comparison with non-CF adult healthy volunteers, Bui and colleagues found no differences in PK parameters between adult CF and non-CF patients after a 30-minute infusion of 2 g of MEM administered every 8 hours (Christensson *et al.*, 1998; Bui *et al.*, 2001). Employing a continuous infusion of 125 and 250 mg/h (3 and 6 g over 24 h, respectively), Kuti *et al.* also measured MEM serum concentrations in 7 adult CF patients, reporting PK parameters similar to those observed by Bui and colleagues, although without comparison with non-CF controls (Kuti *et al.*, 2004a). Notably, all patients included in these studies were given MEM while in good health, during inter-exacerbations periods (Kuti *et al.*, 2004a; Christensson *et al.*, 1998; Bui *et al.*, 2001). To the best of our knowledge, the PK of MEM during pulmonary exacerbation in adult CF patients has been explored so far only in two case reports, in which the PK parameters of the drug were assessed during an extended 3-hour infu-
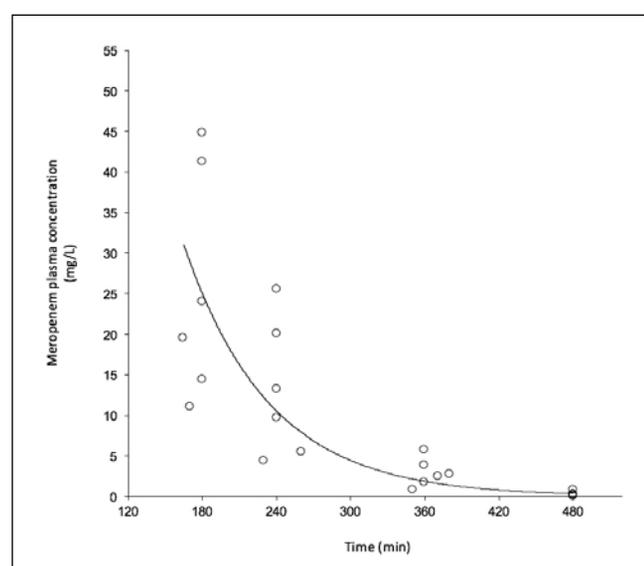

Figure 1 - *Pharmacokinetic profile of high-dose extended infusion meropenem in adult CF patients with pulmonary exacerbation. The drug was administered as an extended 3-hour infusion at a dosage of 2 g every 8 hours.*

Table 2 - *PK parameters of MEM administered as an extended infusion in 6 adult CF patients with pulmonary exacerbation.*

Patient no.	Dose	Tinf min	C_{max} mg/L	AUClast mg/L*h	$AUC_{0-\infty-obs}$ mg/L*h	$T_{1/2}$ min	Ke 1/min	MRT min	CL L/min	Vd L	T>MIC % (Pa MEM MIC)
1	2 g tid	180	14.44	47.38	49.52	89.32	0.008	150.00	0.70	90.67	113 (1 mg/L)
2	2 g tid	180	41.34	120.99	121.20	37.60	0.018	117.22	0.28	14.95	31 (8 mg/L)
3	2 g tid	180	19.55	67.50	67.74	41.71	0.017	125.16	0.49	29.71	60 (1 mg/L)
4	2 g tid	180	24.02	66.54	66.97	50.36	0.014	121.25	0.50	36.40	60 (2 mg/L)
5	2 g tid	180	11.05	29.90	30.13	54.53	0.013	113.06	1.12	87.72	95 (0.25 mg/L)
6	2 g tid	180	44.83	141.70	142.65	48.36	0.014	124.41	0.24	16.41	74 (2 mg/L)
Mean	-	-	25.87	79.00	79.70	53.65	0.014	125.18	0.55	45.98	-
SD			14.09	43.34	43.26	18.51	0.004	12.98	0.32	34.45	

PK, pharmacokinetics; MEM, meropenem, tid, *tris in die* (every 8 h); Tinf, length of infusion; Cmax, maximum plasma concentration; AUClast, area under the plasma concentration-time curve, from 0 to 8 hours postdose; $AUC_{0-\infty-obs}$, area under the plasma concentration-time curve to infinity, based on the last observed concentration; $T_{1/2}$, terminal elimination half-life; Ke, elimination rate constant; MRT, mean residence time; CL, clearance; Vd, volume of distribution; T>MIC, time above the MEM MIC of the last *Pseudomonas aeruginosa* isolated from sputum before/during exacerbation; SD, standard deviation; *Pa, Pseudomonas aeruginosa*.

Table 3 - *Achievement of different % T>MIC according to hypothetical MIC levels in 6 adult cystic fibrosis patients with pulmonary exacerbation due to Pseudomonas aeruginosa treated with high-dose meropenem administered as an extended 3-hour infusion.*

T>MIC	MIC* (mg/L)						
	0.25	0.5	1	2	4	8	16
40%	6 (100)	6 (100)	6 (100)	6 (100)	4 (67)	1 (17)	0 (0)
50%	6 (100)	6 (100)	6 (100)	4 (67)	2 (33)	0 (0)	0 (0)
60%	6 (100)	6 (100)	6 (100)	3 (50)	0 (0)	0 (0)	0 (0)
70%	6 (100)	6 (100)	3 (50)	2 (33)	0 (0)	0 (0)	0 (0)
80%	6 (100)	4 (67)	2 (33)	1 (17)	0 (0)	0 (0)	0 (0)
90%	5 (83)	3 (50)	2 (33)	0 (0)	0 (0)	0 (0)	0 (0)

Values are expressed as number of patients (%). MIC, minimum inhibitory concentration; T>MIC, time above MIC.
*According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST breakpoint tables, Version 7.1, 2017; www.eucast.org), *P. aeruginosa* susceptibility to meropenem is categorized as follows: MIC ≤2 mg/L, susceptible; MIC 4-8 mg/L, intermediate; MIC>8, resistant.

sion of 2 and 3 g every 8 hours, respectively (Bulik *et al.,* 2010; Kuti *et al.,* 2004b). Differently from these reports and from the above-mentioned studies conducted in good health, an apparently very high V_d was observed in the six adults CF patients with pulmonary exacerbation included in our study (mean 45.98 L, SD ±34.45). Besides this, an increase in meropenem clearance (CL) was observed in our patients (mean 0.55 L/min, SD ±0.32), even though their creatinine clearance (CrCl) remained in the normal range. In previous literature data, various hypotheses have been formulated to explain similar increases in meropenem CL in CF patients (Christensson *et al.,* 1998; Pettit *et al.*, 2016; Thomson *et al.*, 2016). For example, peculiar alterations in the function of ion channels and transporters occur in CF patients that might partly account for the observed discrepancy between meropenem CL and CrCl (Staruschenko, 2012). It is thus likely that factors other than glomerular filtration contribute variously in influencing meropenem CL in CF patients, deserving further investigation.

Although no definite conclusion can be drawn in view of our small sample size, we think our results nonetheless highlight the need for further investigation, in order to verify and clarify any possible difference in PK parameters between exacerbation and inter-exacerbation periods that might influence the effectiveness and tolerability of MEM in adult CF patients.

Regarding the achievement of plasma PK/PD targets, in the two cases reported above it was observed that high-dose, extended infusion, MEM could achieve the minimal target of 40% T>MIC in plasma for MICs up to 16 mg/L in two adult CF patients with pulmonary exacerbation (Bulik *et al.,* 2010; Kuti *et al.,* 2004b). In contrast, but similarly to what was observed by Bui *et al.* in patients in good health (Bui *et al.*, 2001), in our study this PK/PD target was largely achievable only for MEM MICs ≤4 mg/L. Although 40% T>MIC was achieved in as many as 5/6 patients in view of the low MEM MICs of their *P. aeruginosa* strains, the possible absence of activity against strains with MEM MIC >4 mg/L might be worrisome in the future, in view of the increasing prevalence of *P. aeruginosa* with high MEM MICs in aged CF patients (Cystic Fibrosis Foundation, 2015; Mustafa *et al.,* 2016). Together with the very low rates of achievement - even for MEM susceptible *P. aeruginosa* - of the much higher PK/PD targets required for severe infections (80-100% T>MIC), this further testifies to the need for larger prospective studies to assess whether increasing doses and/or monitoring drug concentrations could be cost-effective strategies to optimize the use of MEM in the adult CF population.

Finally, particular attention should be paid to the unusually high median age of the adult CF patients included in our study (47 years). Our cohort is indeed considerably older than the other populations of adult CF patients reported

in the literature (Kuti *et al.*, 2004a; Christensson *et al.*, 1998; Bui *et al.*, 2001). Since a prolonged survival of adult CF patients is just a recent success of modern medicine, the effect of ageing on the PK/PD of antimicrobials in this population has yet to be comprehensively investigated. In this regard, pending confirmatory studies, we cannot exclude that age itself had a significant influence on the PK parameters of MEM and their variability in our cohort.

The major limitations of our study are its small sample size and the absence of control groups, both of healthy non-CF patients and of CF patients during inter-exacerbation periods. However, the aim of our preliminary analysis was simply to describe the PK characteristics of MEM in a population of adult CF patients with high median age, in order to provide baseline information for the appropriate design of future case-control studies.

In conclusion, high-dose, extended-infusion MEM was well tolerated in six adult CF patients with pulmonary exacerbation and high median age. Despite a high inter-patient variability of PK parameters, a minimal PK/PD target of 40%T >MIC with respect to their *P. aeruginosa* sputum isolates was largely achievable for MEM MICs ≤4 mg/L. Further studies are needed to assess the effectiveness and tolerability of different MEM dosages, and to further enrich our understanding of the PK/PD of MEM in ageing CF patients.

Conflicts of interest

The authors declare that there are no conflicts of interest relevant to this paper.

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