

Cefiderocol, the first catechol-cephalosporin

José Ramón Azanza Perea¹
Belén Sádaba Díaz de Rada²

Pharmacokinetics/Pharmacodynamics and tolerability of cefiderocol in the clinical setting

¹Departamento de Farmacología, Universidad de Navarra

²Servicio de Farmacología Clínica. Clínica Universidad de Navarra

Revista Española de Quimioterapia
doi:10.37201/req/s02.04.2022

ABSTRACT

Cefiderocol is a new cephalosporin with a catechol in its chemical structure facilitating its access to the interior of bacteria through iron channels. In addition, it is broadly stable to beta-lactamases. The pharmacokinetic profile is a beta-lactam one: no oral absorption, and with a wide distribution within the vascular space and the interstitial fluid of well vascularized tissues, reaching therapeutic concentrations in the alveolar lavage fluid and within the macrophage. The binding of cefiderocol to human plasma proteins, primarily albumin, is moderate (range 40–60%). The terminal elimination half-life in healthy adult subjects was 2 to 3 hours. Cefiderocol is mainly renally eliminated, so dose adjustments are recommended in subjects with moderate / severe renal impairment, in case of dialysis, and probably in patients with external clearance. Like other beta-lactams, the PK / PD parameter that has been shown to best correlate with efficacy is the efficacy time of unbound plasma concentrations (%fT>MIC), which must be close to 100% to achieve a bactericidal effect. This is possible with 2 g in a 3-hour infusion every 8 hours. In controlled trials appears to be well tolerated, similar to comparators: meropenem or imipenem-cilastatin. Cefiderocol has no apparent clinically significant effect on ECG parameters nor on plasma iron values.

Keywords: Cefiderocol; pharmacokinetic; pharmacodynamic, tolerability

INTRODUCTION

The availability of a new antibiotic is, a priori, good news, since it represents an opportunity to potentially confront the advance of bacterial resistance. If, as is the case, the antibiotic seems to be characterized by its activity profile against this

type of bacteria, the news can become transcendental.

Cefiderocol, at least due to its mechanism of action and antibacterial spectrum, can be clearly included in this group of drugs, so having the opportunity to review its pharmacokinetic (PK), pharmacodynamic (PD) and tolerability properties seems a magnificent opportunity.

CHEMICAL STRUCTURE

Cefiderocol (S-649266) is a cephalosporin with a very original chemical structure since it has a chlorocatechol ring that gives it the capacity to penetrate bacteria through iron channels. It is an aminothiazole-cephalosporin with a methoxymine group, common among third and fourth generation cephalosporins [1,2]. It has a molecular weight of 752.2 g/mol and a logP of -2.26. Its chemical name corresponds to (6R,7R)-7-[[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetyl]amino]-3-[[1-[2-[[2-chloro-3,4-dihydroxybenzoyl]amino]ethyl]pyrrolidin-1-ium-1-yl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

PHARMACOKINETICS

Cefiderocol is not absorbed after oral administration and is only available for intravenous parenteral administration.

The behaviour of the drug has been evaluated in different single [3] or multiple [3–5] dose studies, obtaining the parameters summarized in Tables 1 and 2.

The conventional dose is 2000 mg every 8 hours administered in a 3-hour extended perfusion. With this regimen and after administration of single and multiple doses, there was no drug accumulation when administered to healthy subjects [3–5].

Distribution. The binding of cefiderocol to human plasma proteins, mainly albumin, ranges from 40–60%. The geometric

Correspondence:
José Ramón Azanza
Departamento de Farmacología, Universidad de Navarra, Spain.
E-mail: jrazanza@unav.es

Pharmacokinetic parameters	100 mg (n=6)	250 mg (n=6)	500 mg (n=6)	1000 mg (n=6)	2000 mg (n=6)
C _{max} (mg/l)	7.76 (7.8)	18.9 (4.9)	46.6 (10.7)	76.4 (4.6)	156 (7.9)
T _{max} (h)	1	1	1	1	1
AUC _{0-inf} (mg*h/l)	17.49 (8.5)	41.94 (6.3)	108.6 (22.7)	168.1 (7.0)	389.7 (9.0)
t _{1/2} (h)	2.00 (1.4)	1.98 (5.5)	2.12 (15.5)	2.26 (5.8)	2.74 (10.2)
Cl (l/h)	5.72 (8.5)	5.96 (6.3)	4.60 (22.7)	5.95 (7.0)	5.13 (9.0)
Ae 0-48(%)	68.4 (3.2)	64 (5.4)	65.8 (16.2)	68.3 (6.0)	61.5 (10.6)

C_{max}: maximum plasma concentration. T_{max}: time to maximum plasma concentration. AUC_{0-inf}: area under the plasma concentration curve. t_{1/2}: elimination half-life. Cl: total clearance. Ae 0-48%: percentage of drug eliminated unchanged in urine.

PK parameter	Single dose	Multiple dose (day 10)	Single dose
	2000 mg in 1-hour infusion	2000 mg in 1 - hour infusion	2000 mg in 3-hour infusion
Number of subjects	6	8	43
C _{max} (mg/l)	156 (7.9)	153 (12.9)	89.7 (20.5)
AUC _{0-inf} (mg*h/l)	389.7 (9.0)	366.5 (14.0)	386.1 (17.2)
Cl (l/h)	-	5.46 (14.0)	5.05 (17.1)
T _{1/2} (h)	2.74 (10.2)	2.72 (21.6)	2.41 (14.0)

C_{max}: maximum plasma concentration. AUC_{0-inf}: area under the plasma concentration curve. Cl: total clearance. T_{1/2}: elimination half-life.

mean of the volume of distribution during the terminal phase in healthy adult subjects after intravenous administration of a single 2000 mg dose of cefiderocol was 18.0 L (CV 18.1 %), similar to the volume of extracellular fluid [3,4,6]. In another study in healthy subjects and in patients with varying degrees of renal impairment, slightly lower volume of distribution values of around 13 litres were reported [7].

The intrapulmonary pharmacokinetics of cefiderocol after administration to healthy volunteers has been evaluated. For this purpose, a single dose of 2000 mg, administered as a one-hour intravenous infusion, was administered to a group of healthy subjects. Each subject underwent bronchoscopy with alveolar lavage (BAL) and collection of material for the determination of drug concentrations. Bronchoscopy was performed at different times; 1, 2, 4 and 6 hours after the start of drug administration. Each group was composed of 5 subjects. The geometric mean concentrations of cefiderocol in BAL fluid in samples drawn 1, 2, 4 and 6 hours after administration were 13.8, 6.69, 2.78 and 1.38 mg/L, respectively. The range of the total BAL concentration/plasma concentration ratio at 6 hours after administration was 0.0927-0.116 while the ratio of the concentration within the alveolar macrophage (AM) to plasma

was 0.00496-0.104. The ratio of AUC in BAL and MA to plasma was 0.101 and 0.0177, respectively, when calculated with the total drug concentration, while that calculated using the free fraction, not bound to proteins, stood at 0.239 and 0.0419, respectively [8].

These data are consistent with those described systematically for any cephalosporin and, therefore, consistent with a typical distribution profile of beta-lactam antibiotics, which is found in the vascular space and in the interstitial fluid of well-vascularized tissues. Therefore, the higher molecular weight of cefiderocol does not significantly influence its distribution characteristics in the different tissue components.

Biotransformation. Cefiderocol undergoes virtually no metabolism since the unmodified drug accounted for 92.3% of the AUC in plasma after administration of a single dose of 1000 mg radiolabeled with [14C], perfused for 1 hour. The predominant metabolite, pyrrolidine chlorobenzamide (PCBA, a degradation product of cefiderocol), accounted for 4.7% of the plasma AUC of total radioactivity, while each of the remaining metabolites accounted for <2% of the plasma AUC of total radioactivity [9].

Renal Function	Dose	Frequency
Mild renal impairment (CrCl ≥60 to <90 ml/min)	2 g	Every 8 hours
Moderate renal impairment (CrCl ≥30 to <60 ml/min)	1,5 g	Every 8 hours
Severe renal impairment (CrCl ≥15 to <30 ml/min)	1 g	Every 8 hours
End stage renal disease (CrCl <15 ml/min)	0,75 g	Every 12 hours
Patients with intermittent haemodialysis ^b	0,75 g	Every 12 hours

^aCalculated with Cockcroft-Gault formula.

^bSince cefiderocol is eliminated by haemodialysis, administer cefiderocol as soon as possible after the end of the haemodialysis session on haemodialysis days.

Elimination. The elimination of cefiderocol is almost entirely active in the urine, with 74.6, 98.5 and 98.7% of the administered dose being detected between 0–6 hours, 0–48 hours and 0–120 hours, respectively, after the administration of 1000 mg. Only 2.8% of the administered dose was excreted in the feces [9].

The geometric mean clearance of cefiderocol in healthy subjects was estimated to be 5.18 (cv 17.2%) l/h and the terminal elimination half-life in healthy adult subjects to be 2 to 3 hours. Cefiderocol exhibits linear pharmacokinetics in the dose range of 100 mg to 4000 mg [3 4,6].

PHARMACOKINETIC IN SPECIAL POPULATIONS

Several studies have been performed to evaluate the population pharmacokinetics of cefiderocol without demonstrating a significant relationship between the PK parameters of cefiderocol and the various covariates evaluated, which included, among others, age, sex, race, or the location of the infection. The exception was renal function, as should be expected for a drug that is almost entirely eliminated in active form in the urine and whose clearance is directly related to creatinine clearance [10,11].

Paediatric population. No pharmacokinetic studies have been published yet with cefiderocol in children or adolescents under 18 years of age, although the efficacy of 60 mg/kg administration every 8 hours in children with cystic fibrosis has been described. A posological recommendation on the safety of the drug in this age group cannot be established at this time [12].

Renal function alterations. The high renal elimination of cefiderocol implies that alterations in renal function, either by increase or reduction, have an important impact on its pharmacokinetics and require the corresponding dosage adjustment.

Renal impairment. The pharmacokinetics of cefiderocol after administration of a single 1000 mg dose has been

evaluated in subjects with mild renal insufficiency, (glomerular filtration rate [creatinine clearance: CrCl] estimated from 60 to <90 ml/min/1.73 m²), moderate renal insufficiency (CrCl of 30–<60 ml/min/1.73 m²), severe renal insufficiency (CrCl < 30 ml/min/1.73 m²) and end-stage renal disease (ESRD) requiring hemodialysis, compared with that present in healthy subjects and therefore with normal renal function (CrCl > 90 ml/min). The geometric mean ratios for cefiderocol AUC in subjects with mild, moderate, severe renal impairment or ESRD without hemodialysis/normal renal function, and their 90 % confidence intervals (CI) were 1.0 (0.8, 1.3), 1.5 (1.2, 1.9), 2.5 (2.0, 3.3) and 4.1 (3.3, 5.2), respectively. As would be expected, the increase in AUC was due to a reduction in drug clearance without a significant change in the volume of distribution. Approximately 60 % of cefiderocol was eliminated by a 3- to 4-hour hemodialysis session [7]. Table 3 describes the dosage adjustment given in the drug's SmPC.

Patients with augmented renal clearance. Simulations using the population pharmacokinetics model demonstrated that the recommended dose adjustment for augmented renal clearance, administering 2000 mg every 6 hours, provides exposures, and time above MIC (%fT>CMI), of cefiderocol comparable to those of subjects with normal renal function [6,10].

Patients with renal replacement techniques. The available information is limited, but data have been published on plasma concentrations in 2 patients receiving cefiderocol while being treated with these techniques, and in both cases the values of the minimum concentration after therapeutic doses (6000 mg) were lower than those described in other patients, being around 15 mg/l (12 and 18 mg/l) [13]. The administration of 1500 mg every 12 h or 1500 mg every 8 hours, respectively, has been recommended in patients submitted to continuous venovenous hemofiltration and continuous venovenous hemodialysis or continuous venovenous hemodiafiltration [14].

Hepatic impairment. Hepatic impairment is not expected to alter the elimination of cefiderocol since hepatic metabolism and excretion play little role in the elimination of the drug.

INTERACTION WITH OTHER DRUGS

The involvement of cefiderocol in interactions with the various CYP450 isoenzymes and with various transporter proteins has been evaluated. Thus, administration of 2000 mg cefiderocol every 8 hours did not affect the pharmacokinetics of furosemide (a substrate of OAT1 and OAT3) or metformin (a substrate of OCT1, OCT2 and MATE2-K). Coadministration of the same dose increased the AUC of rosuvastatin (a substrate of OATP1B3) by 21%, which was not considered clinically significant or relevant and therefore no dose adjustment was required in any of the cases evaluated [15].

Cefiderocol induces CYP3A4 *in vitro* [4,6], therefore, the metabolism of drugs that are CYP3A4 substrates when co-administered, may increase and lead to an increase in their clear-

ance with a corresponding reduction in systemic exposure. In relation to these facts when cefiderocol is co-administered with CYP3A4 substrates, patients should be monitored for a reduction in the efficacy of the drug whose metabolism may have been induced. Since CYP3A4 induction in vitro by cefiderocol is mediated by pregnane X receptor (PXR), other PXR-inducible proteins, e.g. CYP2C family and P-glycoprotein (Pgp), may also be induced, the clinical relevance of the induction is so far unknown. As a consequence, if cefiderocol is administered together with CYP2C family or Pgp substrates, patients should be monitored for reduced efficacy of the concomitant drug. Based on in vitro studies and a phase 1 clinical evaluation, no significant drug-drug interactions are anticipated between cefiderocol and substrates or inhibitors of cytochrome P450 (CYP) enzymes or intestinal, renal, or hepatic drug transporters [6].

STABILITY

Chemical, microbiological, and physical stability has been demonstrated after dilution, for 6 hours at 25°C and for 24 hours at temperatures of 2 and 8°C. If protected from light it can be stable for more than 6 hours at 25°C [6].

PHARMACODYNAMICS

Cefiderocol is a siderophore cephalosporin with in vitro activity against most Gram-negative bacteria resistant to other drugs, including carbapenemase-producing bacteria. The drug is able to passively diffuse through outer membrane porin channels, binding to extracellular free iron through its siderophore side chain, allowing active transport into the periplasmic space by siderophore uptake systems. Subsequently, cefiderocol will bind to penicillin-binding proteins (PBPs), inhibiting the synthesis of the bacterial peptidoglycan cell wall, resulting in lysis and cell death [16,17].

The activity of cefiderocol against Gram-positive or anaerobic bacteria is small or null due to intrinsic resistance.

In vitro studies have shown that there is no antagonism between cefiderocol and amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, clindamycin, colistin, daptomycin, linezolid, meropenem, metronidazole, tigecycline or vancomycin [6].

The critical values of the minimum inhibitory concentration established by the European Committee on Antibiograms (EUCAST) for cefiderocol are ≤ 2 g/ml for *Enterobacterales* and *Pseudomonas aeruginosa* [6].

PHARMACOKINETICS/PHARMACODYNAMICS RELATIONSHIP (PK/PD)

It has been demonstrated, in mouse infection models, that the parameter that best correlates with the efficacy of cefiderocol is the time during which plasma concentrations of non-protein-bound cefiderocol exceed the minimum inhibitory concentration ($fT\%>CMI$) [18–21].

A study carried out in rats with respiratory infection produced by two strains of *P. aeruginosa*, one susceptible and the other resistant to cephalosporins; 2 strains of *Acinetobacter baumannii* resistant and two strains of *Klebsiella pneumoniae* resistant to carbapenems, showed that the administration of cefiderocol at doses that allowed reaching concentrations similar to those achieved in humans with 2000 mg every 8 h in a 3-hour perfusion for 4 days, produced a reduction of $3\log_{10}$ in the number of viable bacteria in the lung, even in the case of carbapenem-resistant strains. When the infusion time was 1 hour, bactericidal activity was observed in all models, although the $3\log_{10}$ reduction was only achieved in three of the five carbapenem-resistant strains, which was related to the need to achieve the highest possible $fT\%>MIC$ and therefore to extend the infusion to three hours [22].

Identical results were obtained in a PK/PD characterization study to which the efficacy of cefiderocol is adjusted, in which it was found, in the mouse model of infection produced by *P. aeruginosa* with resistance to carbapenems, that the best correlation was achieved with the highest values of the efficacy time of the free fraction ($fT\%>CMI$) compared to the remaining PK/PD parameters; ratio of maximum plasma concentration to MIC (C_{max}/MIC) or area under the curve of plasma levels to MIC (AUC/MIC) [23].

PK/PD behavior of cefiderocol has been evaluated in the treatment of the neutropenic mouse after administration of cyclophosphamide; 150 mg/kg for 4 days, and subsequent inoculation of *Pseudomonas aeruginosa* showing an MIC between 0.63 and 0.5 0.063–0.5 mg/L. Cefiderocol was administered subcutaneously, with dose escalation between 4.2–166.7 mg/kg every 8 h. Dose-response curves were performed on the eight isolates evaluated which showed a sigmoidal pattern with gradually increasing reduction in the number of choline-forming units with the highest doses. The percentage of time during which free drug concentrations exceeded MIC ($fT\%>MIC$) for bacteriostatic effect and 1 log₁₀ and 2 log₁₀ reduction ranged from: 44.4–94.7, 50.2–97.5 and 62.1–100, respectively [24].

A PK/PD analysis involving a Monte-Carlo simulation verified the probabilities of reaching the target (PTA) of the percentage of the interval during which the plasma concentration was higher than the MIC ($fT\%>MIC$) for a range of concentrations from 0.25 to 16 mg/L. Pharmacokinetic parameters previously determined in patients with varying degrees of impaired renal function were used to perform these simulations. The dose of 2000 mg every 8 hours administered as a 3-hour infusion provides a 75% probability of achieving a $fT\%>MIC$ for an MIC ≤ 4 mg/L for patients with normal renal function, whereas more frequent administration (every 6 hours) appears to be required when the patient has elevated renal function. The dose should be reduced or the interval increased in patients with varying degrees of impaired renal function. Finally, it seems necessary to administer a supplementary dose immediately after the end of the hemodialysis session [25].

Recently, the results of a population pharmacokinetic model using 3,427 samples of plasma levels of cefiderocol

Table 4	Cefiderocol. Adverse reactions [6]
<ul style="list-style-type: none"> - Infections and infestations: Candidiasis, including oral candidiasis, vulvovaginal candidiasis, candiduria and yeast infection, <i>Clostridioides difficile</i> colitis, including pseudomembranous colitis and <i>Clostridioides difficile</i> infection. - Immune system disorders*: Hypersensitivity, including skin reactions and itching - Respiratory, Thoracic and Mediastinal Disorders: Coughing - Gastrointestinal disorders: Diarrhea, nausea, vomiting - Skin and subcutaneous tissue disorders: Rash, including macular rash, maculopapular rash, erythematous rash and drug eruption - General disorders and administration site changes Infusion site reaction, including pain at the infusion site, pain at the injection site, erythema at the infusion site and phlebitis at the injection site. - Additional tests: elevated alanine aminotransferase, elevated gamma-glutamyltransferase, elevated aspartate aminotransferase, altered liver function, including increased levels on liver function tests, elevated liver enzymes, elevated transaminases, and liver function test abnormalities. 	

Frequent ($\geq 1/100$ to $< 1/10$) *Rare ($\geq 1/1,000$ to $< 1/100$).

obtained in 91 patients without infection and 425 patients presenting with pneumonia, BSI, sepsis or complicated urinary tract infection have been published. The estimate of the time during which plasma concentrations were above the MIC was 100% in most of the patients evaluated; the probability of reaching a value of 100% was $> 90\%$ for all patients except those with sepsis or BSI and normal renal function, where it was 85% [11].

TOLERABILITY

Cefiderocol is a cephalosporin and as such has the usual adverse effect profile of the group, as has been shown in the pivotal clinical trials in which it was compared with meropenem [26], imipenem [27], or with the best antibiotic in the investigator's judgment [28].

A meta-analysis including the results of the three controlled trials of cefiderocol demonstrated the absence of statistically significant differences in the incidence of adverse effects between cefiderocol and the comparators [29].

A review of the technical data sheet of cefiderocol clearly reflects its beta-lactam profile in terms of tolerability, since the typical adverse effects are described, a summary of which is shown in Table 4.

A consequence of this good tolerability of the drug is the absence of contraindications other than a history of hypersensitivity to beta-lactams and cephalosporins [6].

Warnings and precautions include the potential risk of *Clostridioides difficile* infection and seizures, again related to class effects typical of cephalosporins [6].

Reconstitution of cefiderocol with saline for intravenous administration involves the administration of 2 g of sodium chloride daily, which should be considered in patients at associated risk [6].

As with any new antibiotic, there is insufficient information regarding the use of cefiderocol in pregnant women. Although animal studies do not suggest direct or indirect harmful effects in terms of reproductive toxicity, it is preferable to avoid the use of this drug during pregnancy. It is also not known whether cefiderocol or its metabolites are excreted in milk, so it should be decided whether it is necessary to interrupt lactation or discontinue treatment after considering the benefit of lactation for the child and the benefit of treatment for the mother.

Since the antibacterial effect of cefiderocol involves its penetration of the bacteria using siderophores, specific iron channels, it was important to verify the overall effect of the drug on iron concentrations among the treated patients. The administration of a single dose slightly modified plasma iron concentrations, which were at the lower limit of the normal range (range, 80 to 199 $\mu\text{g/dl}$ for men and 70 to 179 $\mu\text{g/dl}$ for women) on day 5 of the 500 mg administration (71.2 $\mu\text{g/dl}$) and on day 8 (68.3 $\mu\text{g/dl}$), and with the 1000 mg dose, only on day 8 (76.8 $\mu\text{g/dl}$). Despite this, no changes were observed in the group of subjects receiving 2000 mg.

In the multiple dose study, administration of cefiderocol for 17 consecutive days in three groups of subjects; 2 groups received 1000 mg/ 8 h and the third 2000 mg with the same interval, the mean values of plasma iron were slightly below the lower range of the limit of normality on days 5, 11, and 17 and 5, 11, 13, 13, 14, and 17, respectively, in each of the groups treated with 1 g every 8 h. The higher dose (2 g) did not produce abnormalities in plasma iron [3].

The impact of cefiderocol on the electrocardiographic QT interval has been evaluated. In the first study, increasing single doses of drug were used in healthy volunteers [3]. In the other crossover study, healthy subjects received single doses of 2000 mg and 4000 mg of cefiderocol perfused over 3 hours, and moxifloxacin 400 mg in single oral doses. No electrocardiographic alterations were observed in any of the subjects receiving cefiderocol [3,5].

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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