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The pharmacokinetics of cefepime in various health conditions: a review article

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ABSTRACT

Cefepime is one of fourth-generation cephalosporins which has been proven to have activity against a wide spectrum of Gram-positive and Gram-negative bacterias. It induces lysis in bacterias by disrupting the cell wall synthesis. In this review, we presented the pharmacokinetic profile cefepime in subjects with various health conditions, such as in healthy adults, in patients with hematological malignancies, in critically ill patients, as well as in patients with renal impairment. According to various studies, such conditions could alter the pharmacokinetic profile of cefepime, especially on the excretion profile. Nevertheless, it is concluded that cefepime could still be given all subjects, either with and without underlying conditions.

ABSTRAK

Cefepime adalah salah satu dari antibiotik golongan *cephalosporin* generasi keempat yang terbukti aktif melawan bakteri Gram-positif dan Gram-negatif secara luas. *Cefepime* dapat menginduksi lisis pada bakteri dengan mengganggu proses sintesis dinding sel. Artikel ini menyajikan profil farmakokinetik dari *cefepime* pada berbagai macam kondisi kesehatan, yaitu pada orang sehat, pasien dengan kelainan darah, pasien yang sedang sekarat, serta pasien dengan gagal ginjal. Berdasarkan dari penelitian-penelitian yang sudah ada, kondisi kesehatan dapat mempengaruhi profil farmakokinetik dari *cefepime*, khususnya pada profil ekskresi. Meskipun begitu, *cefepime* tetap dapat diberikan kepada segala jenis kondisi kesehatan.

INTRODUCTION

Since the late 19th century, scientists have been searching for ways to kill disease-causing germs. The term of ‘antibiotics’ is used to describe chemicals with the ability to kill or inhibit microorganisms within the body, along with six other properties. There are other six properties to be fulfilled in order for a chemical to be regarded as an antibiotic. First, the chemica must be selective, i.e it will only cause minimum harm to the host cells. Second, it must be soluble in water, so its effectiveness is increased due to the easy transportation through body fluids to the infected sites. Third, it should give minimum side reactions. Fourth, it should be stable, both in shelf-stability (antibiotics which have a long shelf life are more economically useful) and biostability (once taken, the antibiotics should remain in the body for sufficient time to carry out its functions). Fifth, the cost manufacturing should be low enough to be affordable for the patients. Sixth, microorganisms should have a low resistance development rate against it. The first scientifically studied antibiotic was penicillin.[1]

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Another antibiotic which is widely prescribed in the world is cephalosporin.[2] It is a class of beta-lactam antibiotics with known activity against a wide spectrum of Gram-positive and Gram-negative bacterias. Based on its spectrum of bacterias, currently there are five generations of Cephalosporin. One of antibiotic classified to the fourth generation is cefepime ($C_{19}H_{24}N_6O_5S_2$) (FIGURE 1), which has an extended spectrum of Gram-negative bacterias, compared to the third-generation cephalosporins. Cefepime could cause lysis and death to its susceptible targets by binding to transpeptidases called penicillin-binding proteins (PBPs) and disrupting the synthesis of bacterial cell walls. Moreover, beta-lactamases are proven to be significantly unable to hydrolyze cefepime and other fourth-generation cephalosporins.[3,4] There are several bacterias which are known to be susceptible to cefepime, as listed in TABLE 1.

TABLE 1. List of bacterias susceptible to cefepime[4]

Bacterias	Gram-positive or Gram-negative
Streptococcus pneumoniae	Gram-positive
Staphylococcus aureus (methicilin-susceptible)	Gram-positive
Streptococcus pyogenes	Gram-positive
Klebsiella pneumoniae	Gram-negative
Haemophilus influenzae	Gram-negative
Pseudomonas aeruginosa	Gram-negative
Escherichia coli	Gram-negative

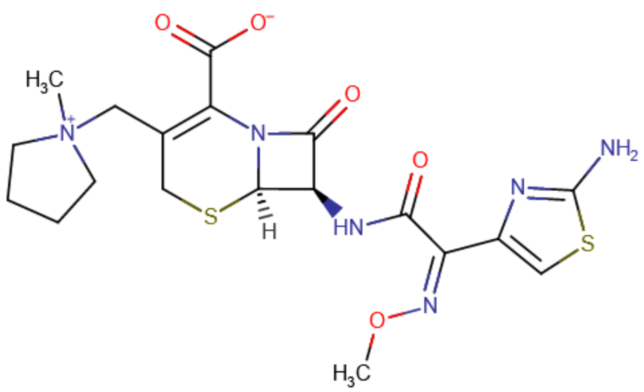

FIGURE 1. The chemical structure of cefepime[4]

Since one of the most important properties of an antibiotic is the biostability, its pharmacokinetic (PK) profile must be analyzed. Moreover, PK profile which is further divided into absorption, distribution, metabolism, and excretion (ADME), is crucial for clinicians to utilize with preclinical data. The physiologically based pharmacokinetic modeling (PBPK) approach allows an interaction map between antibiotics with each organ of the human body to understand its valid extrapolation and the overall system behavior.[5] This technique can evaluate drug-drug interactions, drug-food interactions, drug-disease interactions, and dose as well as the effects of physiological factors on drug PK.[5,6]

Cefepime can be administered via intravenous (IV) and intramuscular (IM) routes, with IV administration reaching peak levels three times higher compared to IM administration.[7] However, various disease states could alter the PK of cefepime. Therefore, this review article provides data and information regarding the PK of cefepime in various health conditions, specifically when given single dose.

Pharmacokinetics of cefepime in various health conditions

In Healthy Subjects

Cefepime binds to albumin at a free fraction (fu) of 61.4% in plasma.[8] Its concentration when administered intravenously reached its peak at ± 30.7 mcg/mL, 30 minutes after 2 g IV dose. When given the same dose through IM, its peak concentration treatment results in a peak concentration of 57.5 ± 9.5 mcg/mL after the same dose. IV administration occurs over a range of 3, 5, 10, 15, 30, 60 minutes, and 3–24 hours. In adults with normal kidney function, the apparent volume of distribution (Vd) is around 0.2 L/kg. Cefepime is dispersed throughout body fluids and tissues. Cefepime clearance (CL) follows first-order kinetics, with its concentration decreasing in a log-linear manner. This process is dependent on kidney function, specifically the glomerular filtration rate.[7] More than 85% of cefepime is excreted unchanged in urine. A small portion of the administered dose is metabolized to produce a metabolite known as N-methylpyrrolidin (NMP), which quickly converts to NMP-N-oxide.[6] However, decreased kidney function could lead to an increased $t_{1/2}$ and decreased CL.

Based on a study conducted by Pais *et al.*,[7] administration of 1 g single dose of cefepime in healthy adult populations resulted in Cmax = 81.7 ± 5.1 mg/L; AUC = 148.5 ± 15.1 mg.h/L; $t_{1/2}$ = 2 ± 0.3 h; and CL = 7.2 ± 0.48 (L/h). Meanwhile, 2 g single dose administration resulted in Cmax = 163.9 ± 25.3 mg/L; AUC = 284.8 ± 30.6 mg.h/L; $t_{1/2}$ = 2 ± 0.3 h; and CL = 7.2 ± 0.48 (L/h). Another study also administered 1 g single dose and resulted in Vd = 14.25 ± 1.35 L; CL = 5.49 ± 1.20 L/h; and $t_{1/2}$ = 1.79 ± 1.32 h.[9] Cefepime is generally well tolerated at clinically relevant doses, ranging from 250 to 2,000 mg every 8 hours for 9 days. Cefepime pharmacokinetics are linear and do not show significant accumulation, even after multiple doses. Cefepime is predominantly excreted via the kidneys with a high renal clearance rate, resembling characteristics of other drugs such as ceftazidime and cefpirome. Cefepime can be administered three times daily to patients with normal kidney function without a significant risk of drug accumulation.[6,8]

In Hematological Malignancies

For patients suffering from hematopoietic cancers or those receiving chemotherapy, the most common and serious complication associated is known as febrile neutropenia. It is characterized as a fever greater than 38.3^{0}C with absolute neutrophil count of <1,500 cells/microliter. Due to lower count of neutrophil, about 50% of febrile neutropenia patients will develop an infection. Gram-positive bacterias are the most common pathogens associated with infections in febrile neutropenia patients, particularly *Staphylococcus aureus* (methicillin-resistant strains) which can cause serious infections.[10]

A study done by Sime *et al.*[11] evaluated the pharmacokinetic of cefepime (with standard dosage of 2 g every 8 hours, administered as a 30-minute infusion) using noncompartmental analysis. Cefepime was given to 12 adult patients with hematologic malignancies and suffered from febrile neutropenia. They concluded that the standard dosage of cefepime provided adequate coverage for organisms with an MIC≤ 4 mg/L, but it might fail if given to organisms with less susceptibility. Whited *et al.*,[12] achieved the same conclusion, by further proving the 99% of remaining free drug concentration in the serum. The noncompartmental analysis utilized by this study resulted in similar mean values, that is AUC of 222.9 mg.h/L and 269 mg.h/L as well as CL of 9.7 L/h and 8.6 L/h, respectively. Moreover, even though Whited *et al.*,[12] opted using compartment analysis to determine K_{el}, its value (0.39/h) was similar to Sime *et al.*,[11] result (0.3/h). However, different values were observed between noncompartmental analysis of these two studies in Vd of 19.2 L and 33.4 L, as well as $t_{1/2}$ of 1.4 h and 2.7 h, respectively.[11,12]

The study done by Rhodes *et al.*,[13] further emphasized the constant result of cefepime pharmacokinetic in patients with febrile neutropenia when they were given the standard dosage, under the condition that all patients have normal renal function. Based on the noncompartmental analysis used in this study, it was estimated that the cefepime had AUC of 240.5 mg.h/L; CL of 8.79 L/h; $t_{1/2}$ of 1.61 h; Vd of 20 L; and K_{el} of 0.28/h. Rhodes *et al.*,[13] also emphasized that cefepime regimens of 3–4 g/day as continuous infusions with doses of 2 g administered as a 30-minute infusion or 2 h infusion is adequate for organisms with MIC≤ 4 mg/L. In addition, an extension of 8 µg/mL MICs can be achieved by giving cefepime infusions of 4 to 24 hours.

In Critically Ill Patients

The recommended standard dosage of cefepime for the critically ill patients is 2 g every 8 hours. However, it is impertinent to adjust the dosage if the critically ill patients have other underlying conditions, such as obesity or suffering from sepsis. Critically ill individuals undergo pathophysiological transformations which can cause a pronounced pharmacokinetic variability, potentially resulting in both insufficient and excessive drug exposure. Failure in dosage adjustment could lead to neurotoxicity in critically ill patients.[14]

One study done to a population of critically ill children evaluated the PK profile of cefepime. Based on this study, it was reported that CL had a value of 1.21 L/h, while Vd had a value of and 4.8 L.[15] Another study done to a population of critically ill adults showed a different value of CL and Vd, i.e 7.84 L/h and 15.6 L, respectively.[16] A latest study done by Junior *et al.*,[17] on critically ill children and young adults showed a value of 6.38 L/h and Vd of 15 L. Although evaluating from the same population, there was a stark difference of CL and Vd values between the study done by de Cacqueray *et al.*,[15] and Junior *et al.*,[17] This is due to the fact that the population studied by de Cacqueray *et al.*,[16] suffered from renal impairment, while Junior *et al.*,[17] excluded such condition in their study. It is interesting to note that there isn't much difference of CL and Vd values between the critically ill children and adults (CL = 7.84 L/h vs 6.38 L/h; Vd = 15.6 L vs 15 L, respectively), as long as they are not suffering from renal impairment.[16,17]

In Renal Insufficiency Patients

Since cefepime is not metabolized, it is eliminated in unchanged form by the kidney. The elimination of cefepime in renal insufficiency patients on dialysis is longer, up to 22 hours. There is a good correlation between creatinine clearance (CLCR) and cefepime clearance (CL) in healthy volunteers with different degrees of renal function. Dosage adjustment needs to be done for patients with renal insufficiency to prevent drug accumulation that may increase risk of adverse drug events and unnecessary increase in drug cost. Only 16–19 % of cefepime hydrochloride is bound to plasma proteins with volume of distribution value 0.25 L/kg and is cleared by dialysis quite effectively.[18]

Dowell *et al*.,[19] compared the PK profile of cefepime (2 g single dose) from renal impairment patients and healthy subjects. The healthy group possessed much lower values in Cmax, AUC, and $t_{1/2}$ compared to the renal impairment group, but higher values in CL and Vd. The values between the healthy group vs the renal impairment group are as follows: Cmax = 102 μg/mL vs 118 μg/mL; AUC = 343 h.μg/mL vs 973 h.μg/mL; $t_{1/2}$ = 2.53 h vs 6.23 h; CL = 5.65 L/h vs 2.64 L/h, and Vd = 20.2 L vs 17.6 L, respectively. Moreover, this study also compared the PK profile of cefepime in renal impairment patients undergoing dialysis and not. The results showed that undergoing dialysis could fasten the clearance of cefepime from the body. Overall, this study showed that renal impairment caused a significant decrease in cefepime systemic clearance. However, hemodialysis could substantially remove the cefepime plasma. A similar result was also obtained in another study, where receiving renal replacement therapy, i.e hemofiltration, could clear cefepime from the body of patients suffering from acute kidney injury with a rate of 24.33 ± 11.25 mL/min.[20] Recent study by Pavia *et al*.,[21] also reported that patients with renal impairment had CL value of 3.0 ± 0.6 L/h, AUC_{24h} of 1695 ± 629 mg.h/L, and Vd of 22.7 ± 8.0 L.[21]

CONCLUSION

Cefepime is mainly excreted in the kidneys, therefore its rate of elimination is proportional to renal function. Various health conditions, i.e. hematological malignancies, critically ill, or renal insufficiency, could alter the PK profile of cefepime. Nevertheless, the standard dose of cefepime (1 g or 2 g single dose) can still be given to patients suffering from hematological malignancies or critically ill, as long as their kidneys remain functional. Cefepime can also be still administered for patients with renal insufficiency, however it is better be accompanied by hemofiltration or hemodialysis to improve its clearance from the body.

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