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CASE REPORT

The importance of pharmacokinetic consultation of cefepime treatment for *Pseudomonas aeruginosa* bacteremia: a case report of severe thermal burn injury

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Abstract The patient is a 54-year-old man with severe thermal burn injury involving 45.5% of the total body-surface area, complicated with bacteremia caused by *Pseudomonas aeruginosa* with a cefepime MIC of 8 μg/ml. The plasma concentrations of cefepime 1 g every 6 h measured by validated high performance liquid chromatography were 25.8 μg/ml at 1 h and 6.28 μg/ml at 5 h after infusion, and 3.9 μg/ml before the infusion, when creatinine clearance was increased to 136 ml/min by vigorous fluid replacement. The pharmacokinetic–pharmacodynamic analyses in the one-compartment model with use of the Sawchuk–Zaske method revealed marked increase in the volume of distribution (28.9 l), total clearance (10.7 l/h), and shortening of plasma half- life (1.79 h) of cefepime, with time >MIC and 24-h area under the concentration–time-curve being 58% and 358, respectively. These pharmacokinetic parameters of cefepime quantified in the patient estimated a time >MIC of 87% if administered every 4 h. *P. aeruginosa*, however, was successfully eradicated without revision of the dosing regimen of cefepime. Decrease in creatinine clearance by correction of the fluid imbalance and wound closure by skin graft surgery likely contributed to the restoration of fluid shift, resulting in normal disposition of cefepime and favorable clinical outcome of the patient.

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Introduction

The pharmacokinetic–pharmacodynamic (PK–PD) parameter that best predicts the therapeutic efficacy of β-lactam antibiotics is the percent time of dosing interval during which free drug concentration exceeds the minimum inhibitory concentration (MIC) for causative pathogens ($t >$ MIC). For cephalosporins, with which the rate of killing of bacteria is the slowest among β-lactams, $t >$ MIC of 60–70% is required for achieving maximum bactericidal effects [1, 2].

Although the integration of population PK–PD data in individual patients, exemplified as the Monte Carlo simulation [3, 4], has provided continued insights into antibiotic regimens [5], careful attention with respect to the alterations in drug disposition should be paid to those patients who have fluid shift and/or overload or increased creatinine clearance that significantly affect the volume of distribution (VD) and renal clearance, which synergistically lower the plasma concentrations of the hydrophilic β-lactam antibiotics.

The increase in VD and total clearance have been reported in thermal burn injury for cefepime [6–8], tazobactam/piperacillin [9], imipenem/cilastatin [10], and aztreonam [11], all of which have good antimicrobial activities against *Pseudomonas aeruginosa*, the most frequently isolated organism contributing to the increase in morbidity and mortality in burn care units [12, 13].

We describe a case of extensive burn injury complicated by bacteremia caused by *P. aeruginosa* with decreased

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antimicrobial susceptibility relative to the pharmacokinetic alterations unique to the patient. The mechanism of impaired disposition of cefepime, and the importance of patient-specific PK–PD application to the assessment of antimicrobial therapy in burn patients, are discussed with review of the literature.

Case report

A 54-year-old man was admitted because of thermal burn injury involving 45.5% of the total body-surface area (BSA), comprising 30.5% deep dermal burn and 15% deep burn, with a prognostic burn index (PBI) of 81.5. He was immediately started on therapy with vigorous fluid resuscitation, excision of burn tissue, and nutritional support. On the 3rd hospital day when the first skin graft was performed, because the patient's body temperature was 38.9°C and the burn wound culture yielded methicillin-sensitive *Staphylococcus aureus*, intravenous cefazolin (CEZ) 1 g every 8 h was started (Fig. 1). However, because he continued to have high fever and leukocytosis on the 8th day and culture from blood drawn at that time grew gram-negative small rods, antimicrobial therapy was switched to cefepime (CFPM) 1 g/30 min every 6 h, followed by the second skin graft surgery on day 9. The positive blood culture subsequently identified *Pseudomonas aeruginosa*, to which the minimum inhibitory concentration (MIC) of CFPM was 8 μg/ml, that was considered barely sensitive by the definition of the Clinical Laboratory Standards Institute [14]. The MIC of ceftazidime was 16 μg/ml, and both meropenem and tobramycin were ≤0.5 μg/ml. Because his body temperature was still high, and WBC was 17,200/μl and C-reactive protein (CRP) was 11.5 mg/dl after 4 days of CFPM treatment, therapeutic drug monitoring was performed, after obtaining an informed consent from the patient, to help differentiate whether the continuing fever and leukocytosis were caused by treatment failure of anti-pseudomonal therapy by CFPM or skin and soft tissue infection with possible intermittent bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) with a vancomycin (VCM) MIC of 1 μg/ml that had been cultured from skin discharge on two occasions.

Using the validated high performance liquid chromatography method [15] with minor modifications, plasma concentration of unbound CFPM measured at 1 and 5 h after the infusion and before the infusion (Cmin) was 25.8, 6.28, and 3.99 μg/ml, respectively. The pharmacokinetic parameters determined in the one-compartment model by the Sawchuk–Zaske method [16] were elimination rate constant (k_{el}), 0.386/h; volume of distribution (VD), 28.9 l = 0.4303 l/kg; total clearance of CFPM (CL_{CFPM}), 10.7 l/h = 0.1662 l/kg/h; and serum half-life ($T_{1/2}$), 1.79 h (Table 1). These values all deviated from the pharmacokinetics of cefepime studied in normal subjects [17–20]. Hence, $t >$ MIC was calculated as 58%, AUC_{0-24} [the area under the plasma concentration-versus-time curve; dose (24 h mg)/CL_{CFPM} (l/h)] as 358, and the AUIC(the area under the inhibitory concentration–time curve)$_{0-24}$/MIC as 45. The maximum concentration (Cmax) of CFPM in regression analyses was estimated at 38 μg/ml (see Table 1). The creatinine clearance (CL_{CR}) on the day of TDM was 136 ml/min (Fig. 1) by the Cockcroft–Gault formula [21].

Although if administered every 4 h instead of 6 h, $t >$ MIC was estimated to be 87%, and $AUIC_{0-24}$ to be 67 (see Table 1), because multiple sets of the follow-up blood cultures drawn when the fluid imbalance was being corrected were negative, CFPM was continued without changing the dosing regimen, while VCM 1 g every 12 h was coadministered, presuming that MRSA infection was present. Although the trough concentration of serum VCM after the sixth dose, when CL_{CR} was 92 ml/min, was 8.5 μg/ml, a lower value than that recommended in the recent guideline [22], the patient became almost afebrile by

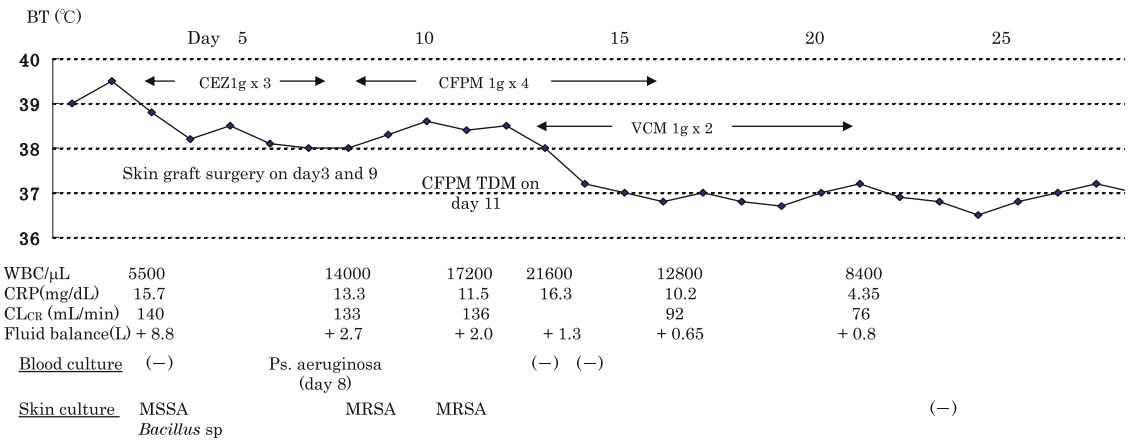

Fig. 1 Clinical course of the case. *Ps. aeruginosa*, *Pseudomonas aeruginosa*

Table 1 Pharmacokinetic–pharmacodynamic parameters of cefepime in burn patients and healthy subjects

	TBSAB (%)	CL_{CR} (ml/min)	Serum conc. (μg/ml)		k_{el} (h^{-1})	CL_{CFPM} (l/h)	VD (l)	$T^{a}_{1/2}$ (h)	AUC (mg/l/h)	$t > MIC$ (%)
			Cmax	Cmin						
Present case	45	136	38.0[b]	3.9[b] (11.5)[e]	0.386[c]	10.7[c]	28.9[c] (0.43 l/kg)	1.79[c]	358[d] (537)[e]	58[d] (87)[e]
Ref [6] ($n = 12$)	31	135 ± 31	110 ± 23	5.5 ± 2.6 at 8 h	NA	8.8 ± 2.4	0.43 l/kg	2.8 ± 0.6	224	45–100
Ref [7] ($n = 6$)	36	123 ± 26	122 ± 23	2.1 ± 1.1	NA	9.1	0.36 l/kg	2.4 ± 0.5	434	NA
Ref [8] ($n = 13$)	21.8	92 ± 39	140 ± 58	17 ± 26	NA	7.1 ± 3.6	0.31 l/kg	2.9 ± 3.2	840	NA
Healthy subjects[f]			65–79	2.9 ± 1.0		7.3–7.5	18 ± 2.0	2.2–2.6	1138 ± 540[g]	

The values of pharmacokinetics (PK) parameters from the previous studies cannot be directly compared because of the difference in the dosage of cefepime and study design. Dosage of cefepime (CFPM): 1 g × 4/day (present case), a single 2-g dose (Ref. [6]), 2 g × 2/day (Ref. [7]), or 2 g × 3/day (Ref. [8])

TBSAB, total body-surface area of burn; NA, not available

[a] $T_{1/2}$ of Refs. [6] and [7] represent $T_{1/2\beta}$

[b] Samples were prepared by ultrafiltration and centrifugation of the plasma, then applied to high performance liquid chromatography consisting of a pump (LC-6A, Shimazu), UV absorbance detection at 280 nm (SPD-6AV, Shimazu), and data integrator (C-R3A, Shimazu). The coefficient of determination by linear regression was 0.9995

[c] Pharmacokinetic parameters were determined based on the Sawchuk–Zaske method [16] with one compartmental model equations for intermittent intravenous infusion

[d] AUC_{0-24} = 24 h-dose (mg)/CL_{CFPM}. % $t > MIC$ = ln [dose/(VD × MIC)] × [$T_{1/2}$/ln (2)] × [100/dosing interval]

[e] Numbers in the parentheses represent the simulated values for CFPM 1 g administered every 4 h

[f] References [17–20]

[g] CFPM 2 g × 2/day; CL_{CR} 60–100 ml/min (Ref. [5])

day 17. The patient's clinical course was uneventful after discontinuation of antimicrobial treatment, and he was discharged from the hospital 2 months after admission.

Discussion

A 50% increase in predicted mortality has been reported in burn patients with gram-negative bacteremia compared to those without bacteremia [23]. The present case was a severe burn patient with a PBI of 81.5 and adjusted predicted mortality rate by APACHE II of 24.5% [24], complicated with *P. aeruginosa* bacteremia.

For *P. aeruginosa*, a CFPM MIC of 8 μg/ml or less is considered susceptible [14]. However, a recent report by Bhat et al. on gram-negative bacteremia treated with CFPM, typically 1–2 g every 12 h, revealed that the rate of 28-day mortality from *P. aeruginosa* bacteremia was significantly higher when isolates had CFPM MIC of 8 μg/ml, compared to those of 4 μg/ml or less (66.7% vs. 20.8%), suggesting that a CFPM MIC of 8 μg/ml, as in our case, should no longer be regarded as susceptible [25].

For β-lactams, $t > MIC$ has originally been considered to require 60–70% for bactericidal effects for cephalosporins [1, 2]. McKinnon et al., with the use of population parameters of VD and CL_{CFPM}, have analyzed the PK–PD parameters of renal function-adjusted equivalent dosing of CFPM (2 g every 8, 12, and 24 h) in relationship to the clinical outcome of 76 patients with bacteremia and sepsis. The rate of bacteriological eradication and clinical cure in a subgroup of patients ($n = 7$) whose $t > MIC$ was less than 80% was 42.8% and 28.6%, respectively [26]. Similarly, the most recent study by Monte Carlo simulation has reported that patients infected with *P. aeruginosa* whose $t > MIC$ was less than 60% were 8.1 times more likely to experience poor microbiological response [3].

In our patient, although $t > MIC$ of CFPM based on the actual measurement of serum concentrations was 58%, a suboptimal value for this agent to exert bactericidal activity [3, 26, 27], the bacteremia caused by *P. aeruginosa* with a CFPM MIC of 8 μg/ml was cured both microbiologically and clinically. Although McKinnon et al. have reported that $AUIC_{0-24} < 250$ was the only predictor of bacteriological failure in sepsis and bacteremia caused by *P. aeruginosa* with MIC range of 1–16 μg/ml (10 strains) [26], the PK–PD analyses in our patient revealed $AUIC_{0-24}$ to be 44.8 with CFPM every 6 h, and 67.1 even with every 4 h. Therefore, in contrast to their findings, AUIC was not a primary indicator of clinical efficacy of CFPM in our patient.

What is yet to be discussed regarding PK–PD alterations of cefepime in the present case is that the estimated Cmax (38 μg/ml) was one-half as high as the generally expected value for 1 g CFPM (65–79 μg/ml) [18, 20]. This finding could be explained by an increase in CL_{CR} and VD. The vigorous fluid resuscitation in our patient likely forced the

glomerular filtration of CFPM. This mechanism is supported by the previous reports on pharmacokinetics of cefepime in burn patients [6–8] that CL_{CFPM} increased in proportion to the increase in creatinine clearance (see Table 1). Mechanical disruption of the skin integrity by extensive burn wounds coupled with hypoalbuminemia likely contributed to synergistically lower the plasma concentration of the hydrophilic CFPM via extravasations of the plasma, and accumulation in the interstitial space, as reflected by a significant increase in VD (28.9 l = 0.43 l/kg) compared to those in healthy subjects and previous studies in burn patients as well (see Table 1). Bonapace et al. [6] have shown that the percent of body-surface area with deep burns is strongly correlated with increase in VD of cefepime ($r^2 = 0.55$; $P = 0.0411$). Sampol et al. have reported that after 12 h following a CFPM dose of 1 g, the concentrations in burned skin tissue were 33 ± 41.4 μg/g (range, 9–115) [7], a finding that lends supports for the presumed mechanism of the increased VD observed in our patient. No doubt that increase in CL_{CR} and VD caused an increase in total clearance of cefepime, resulting in the shortening of plasma half-life and suboptimal $t > MIC$ (Table 1). Thus, CFPM in our patient was probably being eliminated during the infusion time.

Therefore, had the $t > MIC$ for CFPM been much lower, the dosing interval of CFPM would have been revised to every 4 h, because our analyses had predicted a significant increase in Cmin and $t > MIC$ (Table 1). Or, replacement of CFPM by meropenem or combination therapy with aminoglycoside could have been another choice.

Whether the clinical improvement in this patient was the result of the eradication of *P. aeruginosa* by CFPM, or the addition of VCM against possible MRSA infection, or both, remains unclear; however, restoration of CL_{CR} together with the wound closure by skin grafts seem to have resulted in maintaining appropriate plasma concentrations of these antibiotics although CFPM concentration was not measured after normalization of CL_{CR}.

In conclusion, antimicrobial therapy with β-lactams including CFPM in severe burn patients should be optimized, if possible, based on the actual measurement of the plasma concentrations, taking into account the alterations in the drug disposition, which could significantly affect the expected bactericidal effects inherent to this class of agent.

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