Adequacy of High-Dose Cefepime Regimen in Febrile Neutropenic Patients with Hematological Malignancies

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While guidelines recommend empirical cefepime therapy in febrile neutropenia, the mortality benefit of cefepime has been controversial. In light of this, recent reports on pharmacokinetic changes for several antibiotics in febrile neutropenia and the consequent suboptimal exposure call for a pharmacokinetic/pharmacodynamic evaluation of current dosing. This study aimed to assess pharmacokinetic/pharmacodynamic target attainment from a 2-g intravenous (i.v.) every 8 h (q8h) cefepime regimen in febrile neutropenic patients with hematological malignancies. Cefepime plasma concentrations were measured in the 3rd, 6th, and 9th dosing intervals at 60% of the interval and/or trough point. The selected pharmacokinetic/pharmacodynamic targets were the proportion of the dosing interval (60% and 100%) for which the free drug concentration remains above the MIC ($fT_{>MIC}$). Target attainment was assessed in reference to the MIC of isolated organisms if available or empirical breakpoints if not. The percentage of $fT_{>MIC}$ was also estimated by log-linear regression analysis. All patients achieved $>60\%$ $fT_{>MIC}$ in the 3rd and 6th dosing intervals. A 100% $fT_{>MIC}$ was not attained in 6/12, 4/10, and 4/9 patients in the 3rd, 6th, and 9th dose intervals, respectively, or in 14/31 (45%) of the dosing intervals investigated. On the other hand, 29/31 (94%) of trough concentrations were at or above 4 mg/liter. In conclusion, for patients with normal renal function, a high-dose 2-g i.v. q8h cefepime regimen appears to provide appropriate exposure if the MIC of the organism is ≤ 4 mg/liter but may fail to cover less susceptible organisms.

The introduction of cefepime into clinical practice was widely accepted due to its broad-spectrum activity. Cefepime is active against such organisms as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* with relatively low MICs compared to those of other broad-spectrum β -lactam antibiotics (1, 2). Therefore, it is considered a good choice for the empirical management of febrile neutropenia, either as a monotherapy agent or as part of combination regimens (3, 4).

While several comparative outcome trials suggest cefepime is clinically as effective as other β -lactam antibiotics, meta-analyses (5, 6) of data from these trials report an increased risk of mortality associated with cefepime therapy, which was particularly high in febrile neutropenic patients (7). Conversely, a later meta-analysis by the U.S. Food and Drug Administration (FDA), which included several additional unpublished trials, concluded that there is no such association (8, 9). In addition, specific analysis of trials of febrile neutropenic patients did not show any statistically significant increase in mortality (9). The controversy continues as the methodological issues of the FDA's and previous meta-analyses are challenged and debated (7, 10–12). However, there is little biological plausibility for the claimed risk of mortality, which was originally suggested to be related to unrecognized toxicity or poor *in vivo* antibiotic efficacy (6). Suboptimal antibiotic concentration and possible pharmacokinetic/pharmacodynamic (PK/PD) explanations were implicated.

PK/PD describes the relationship between the dose of antibiotics, the resulting concentrations achieved in biological fluids, such as plasma or interstitial fluid, and the associated antibacterial

activity. Characteristic relationships exist between plasma concentrations and antibacterial activity. For β -lactam antibiotics, including cefepime, the duration of the dosing interval for which the free drug concentration remains above the MIC ($fT_{>MIC}$), is the PK/PD index that guides dose selection and objectively measures dosing adequacy (13). For cefepime and other cephalosporins that exhibit the least postantibiotic effect among the β -lactams, 60 to 70% $fT_{>MIC}$ is the conventional conservative PK/PD target (13), even though 100% $fT_{>MIC}$ may be required in immunocompromised hosts (14).

Any changes in the PK or PD properties of antibiotics demand adjustment of the dosing regimen to ensure attainment of the required PK/PD target (15). The PK of antibiotics is amenable to pathophysiology-driven alterations in some special patient populations with marked infections or inflammation, including those

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with neutropenic fever and malignancy. PK changes are observed as increases in the volume of distribution and/or clearance and subsequent low plasma and tissue concentrations. The PD response may be affected due to changes in bacterial susceptibility. Such PK/PD changes in febrile neutropenic patients are documented for β -lactam antibiotics (16), although there is a dearth of information on cefepime. Navas et al. (17) have reported inadequate exposure from a traditional cefepime regimen (2 g intravenous [i.v.] every 12 h [q12h]) in febrile neutropenic patients. However, a higher dosing regimen (2 g i.v. every 8 h [q8h]) is now more commonly used in neutropenic patients with normal renal function. The objective of this work was therefore to assess PK/PD target attainment from an intermittent 2-g i.v. q8h cefepime dosing regimen in febrile neutropenic patients with hematological malignancies.

MATERIALS AND METHODS

Study setting, patients, and drug administration. The study was conducted at The Queen Elizabeth Hospital (TQEH), Adelaide, South Australia. TQEH is an acute care teaching hospital providing emergency, inpatient (311 beds), outpatient, and mental health services for a population of over a quarter of a million. Patients aged ≥ 18 years were preconsented while receiving chemotherapy and/or stem cell transplant at the hematology unit of TQEH for the management of hematological malignancies. Thereafter, patients were enrolled when they developed febrile neutropenia, which was defined as the presence of a single oral temperature of $\geq 38.3^\circ\text{C}$ (101°F) or a temperature of $\geq 38.0^\circ\text{C}$ (100.4°F) for >1 h or with a neutrophil count of <500 cells/ mm^3 or a count of $<1,000$ cells/ mm^3 with a predicted decrease to <500 cells/ mm^3 (18). Additional inclusion criteria were prescription of cefepime for the management of febrile neutropenia and the presence of a peripherally inserted central catheter (PICC) for blood sampling. Patients were excluded if they had a known or suspected allergy to cefepime, did not have a PICC line, or were pregnant. The study was conducted in accordance with an Australian national statement on ethical conduct in human research as well as the Declaration of Helsinki. Ethics approval was granted by the Human Research Ethics Committees of TQEH (HREC/13/TQEHLMH/301) and the University of South Australia (application ID 0000032581).

All patients received 2 g cefepime administered every 8 h via intermittent i.v. infusion over 30 min, followed by 15 min of line flushing. In addition, all patients received gentamicin (7 mg/kg of body weight once daily) for 1 to 3 days.

Data collection and blood sampling. Data describing patient characteristics were collected from electronic or paper-based medical records and included the following: demographic characteristics, diagnosis of malignancies and infections, microbiological data, vital signs, and clinical hematological and chemistry data. Five blood samples were taken per patient over 3 days to monitor assumed steady-state cefepime concentrations. The first two samples were taken after the third dose: one at 60% of the dosing interval and the other as a trough 15 min before the next dose. The next two samples were taken similarly in the sixth dosing interval, and finally, one trough sample was taken at the end of the ninth dosing interval.

Drug assay. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method previously validated for simultaneous analysis of β -lactam antibiotics (19) was extended to include cefepime on an ultraperformance liquid chromatography system (Shimadzu Corp., Kyoto, Japan) connected to an API3200 mass detector (AB Sciex Pte., Ltd.). The sample preparation procedures and mobile phase systems were as formerly described. Chromatographic separation was achieved on a C_{18} column (Zorbax Eclipse XDB- C_{18} , 2.1 mm by 150 mm, 3.5 μm ; Agilent Technologies, Inc.) via gradient elution. Multiple reactions monitoring (MRM) was performed in a positive mode using electrospray ionization. The masses of precursor and product ions monitored for cefepime were

481.1 and 125.0, respectively. Piperacillin was used as an internal standard with MRM charge/mass ratios (m/z) of 518.16/143.10. Quadratic regression with a weighting scheme of $1/(x \times x)$ best described the data for calibration curves over the concentration range of 0.25 to 50 mg/liter ($r^2 > 0.9$). The lower limit of quantification was 0.25 mg/liter. The interday and intraday mean accuracies of quality control samples (QCs) ranged from 99% to 105% and 99% to 110%, respectively. Intraday and interday coefficients of variation were less than 15% at all QC concentrations. The mean recovery was 95%. Stability data over three freeze-thaw cycles, for 4 h on the benchtop as well as for 12 h postpreparation, were within the requirement guidelines (20).

Pharmacokinetic analysis. First, considering log-linear PK (21), concentrations at 0.75, 2, 4, and 6 h were estimated based on the two concentrations measured in the third dosing interval. Then the resulting concentration-time profiles, including the measured concentrations, were used to perform noncompartmental PK analysis using an MS Excel add-in program, PK Solver (22). The value 0.5 h was entered for the (bolus) infusion time, and the linear trapezoidal method was selected for calculation of the area under the curve from 0 to infinity ($\text{AUC}_{0-\infty}$).

Statistical analysis. IBM SPSS Statistics version 19.0 (SPSS, Inc., Chicago, IL) software was used to execute statistical analysis. Characteristics of study participants were summarized using descriptive statistics. As appropriate, the Mann-Whitney U test or Kruskal-Wallis test was used to compare observed concentrations among the dosing intervals. A P value of <0.05 was considered statistically significant.

Pharmacodynamic assessment. The blood sampling times were selected to enable assessment of the achievement of $60\% fT_{>\text{MIC}}$ and $100\% fT_{>\text{MIC}}$ without calculating the exact duration for which the free concentration remains above the MIC. Free cefepime concentrations were calculated from total plasma concentration assays considering 19% protein binding (23, 24). When culture tests were positive, specific MICs for the isolated organisms were used if available. When there were no organisms identified, the highest MIC of all susceptible organisms (8 mg/liter) was used according to the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints (25, 26). Additionally, the percentage of $fT_{>\text{MIC}}$ was estimated for the third and sixth dosing intervals by means of log-linear regression analysis based on the two concentrations measured in the terminal elimination phase.

RESULTS

Twelve patients with neutropenic fever and malignancy were enrolled in the study. Characteristics of these study participants are presented in Table 1. Most patients exhibited slight hypoalbuminemia and did not have renal dysfunction. Blood cultures tested positive for four patients. Two patients were obese, four patients were overweight, and the rest had normal body weight.

Fifty-three plasma concentrations were analyzed from the 12 patients in 31 assumed steady-state dosing intervals. For two patients, only two concentrations each were measured during the third dosing interval, and for one patient, a concentration was not measured after the sixth dosing interval because cefepime was discontinued by clinicians treating the patient. PK parameter estimates for all patients are summarized in Table 2. Figure 1 depicts the distribution of free plasma cefepime concentrations measured at 60% of the dosing interval in the third and sixth dosing intervals. All concentrations were above the highest MIC of susceptible organisms (8 mg/liter), and hence $>60\% fT_{>\text{MIC}}$ was attained in all patients. A comparison of unbound trough cefepime concentrations from all participants in the third, sixth, and ninth dosing intervals is presented in Fig. 2. No statistically significant difference in trough concentrations was noted among the three dosing intervals ($P = 0.975$), although the median value was relatively

TABLE 1 Characteristics of study participants

Patient no.	Sex ^a	Age (yr)	Wt (kg)	BMI (kg/m ²)	Hematological malignancy	Creatinine clearance (ml/min/1.73 m ²) ^b			Serum albumin value (g/liter)			Blood culture result
						Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	
1	M	54	75	21.3	Hodgkin's lymphoma	87	79	70	23	24	27	<i>Staphylococcus</i> spp.
2	M	79	86	28.9	Diffuse large B-cell lymphoma	89	68	72	31	30	32	<i>Bacillus</i> spp.
3	M	52	96	27.7	Acute myeloid leukemia	66	74	81	30	28	30	<i>Klebsiella pneumoniae</i> , <i>Enterococcus faecium</i>
4	F	59	67	23.5	Follicular lymphoma	88	73	68	32	32	32	Negative
5	F	76	64	23.8	Acute myeloid leukemia	61	61	66	25	26	28	Negative
6	M	50	75	25.4	Diffuse large B-cell lymphoma	64	55	55	29	31	29	Negative
7	M	56	88	23.6	Mantle cell lymphoma	72	72		28	30		<i>Bacillus</i> spp.
8	M	57	77	25.7	Multiple myeloma	72	63	72	32	29	31	Negative
9	M	66	86	29.8	Multiple myeloma	69	69	60	29	27	31	Negative
10	M	39	184	46.9	Diffuse large B-cell lymphoma	65	65	65	30	31	32	Negative
11	M	68	101	33.7	Anaplastic large cell lymphoma	75	83	83	29	24	24	Negative
12	F	40	73	29.4	Acute myeloid leukemia	106	101	101	27	27	27	Negative
Median (IQR) ^c		57 (52–67)	82 (74.5–90)	26.7 (23.8–29.5)		72 (66–88)	70 (65–75)	70 (66–77)	29 (28–30)	29 (27–30)	30 (28–32)	

^a M, male; F, female.^b Creatinine clearance estimated by the Cockcroft-Gault equation.^c IQR, interquartile range.

TABLE 2 Noncompartmental pharmacokinetic parameter estimates of cefepime from 12 febrile neutropenic patients with hematological malignancies

Parameter ^a	Mean	Median	IQR ^b
V_{ss} (liters/kg)	33.4	34	24.8–42.7
CL (liters/h)	8.6	8.7	6.8–10.8
$t_{1/2}$ (h)	2.7	2.5	2.4–3.0
MRT (h)	3.9	3.6	3.5–4.4
$AUC_{0-\infty}$ (mg/liter · h)	269	232	186–294
k_{el} (1/h)	0.3	0.3	0.2–0.3

^a V_{ss} , volume of distribution at steady state; CL, total clearance; $t_{1/2}$, half-life; MRT, mean residence time; $AUC_{0-\infty}$, area under the concentration versus time curve from time zero to infinity; k_{el} , terminal elimination rate constant.
^b IQR, interquartile range.

higher in the sixth dosing interval. Nearly half of the unbound trough concentrations, 14/31 (45%), were below 8 mg/liter (the highest MIC). In contrast, 29/31 (94%) of trough concentration were at or above 4 mg/liter. No trough concentration less than 2 mg/liter was observed. The distributions of percentages of $fT_{>MIC}$ estimates in the third and sixth dosing intervals are depicted in Fig. 3. Six of the 12 patients during the third interval, 4/10 patients during the sixth interval, and 4/9 patients in the ninth interval did not achieve 100% $fT_{>MIC}$. However, the percentages of $fT_{>MIC}$ were greater than 70% and 60% for all patients in the third and sixth dosing intervals, respectively.

DISCUSSION

In the context of the growing evidence of altered antibiotic PK and subsequent underexposure in febrile neutropenia, a high-dose cefepime regimen (2 g i.v. q8h) has not been widely subjected to PK/PD assessment. In addition to this, a clear picture is lacking with regard to the underlying causes of the controversial claims of

FIG 1 Box-and-whisker plot of unbound cefepime plasma concentrations at 60% of the third and sixth dosing intervals in febrile neutropenic patients with hematological malignancy receiving 2-g i.v. q8h dosing. The whiskers extend to 1.5 times the interquartile range from Q1 or Q3, or the highest/lowest point within the range. Outlier points are those that are away from the interquartile range by greater than 1.5 times from Q1 or Q3. The black and gray areas represent the distances from the 1st quartile to the median and from the median to the 3rd quartile, respectively.

FIG 2 Unbound cefepime plasma concentrations from trough samples in the third, sixth, and ninth dosing intervals in patients with neutropenic fever and hematological malignancy receiving 2-g i.v. q8h dosing.

increased risk of mortality associated with cefepime therapy, except for thoughts of the potential role of toxicity as well as underexposure from conventional dosing (6, 27). Although this study did not aim to describe cefepime toxicities, it evaluated PK/PD exposure from a 2-g dose administered q8h via intermittent i.v. infusion in febrile neutropenic patients with malignancies.

The median volume of distribution of cefepime estimated in this study is higher than that reported for healthy individuals from a phase I study (34 liters versus 18 liters) (21). Similarly high mean/median volumes of distribution have been previously reported for critically ill patients (27) ($\approx$ 29 liters), burn patients (28) ($\approx$ 26 liters), and general ward patients with normal renal function (29) ($\approx$ 32 liters). The observed significant expansion in volume of distribution may be attributable to a combination of various factors, including capillary fluid extravasation, high-volume fluid therapy, and the markedly increased body mass index

FIG 3 Box-and-whisker plot of proportions of the dosing interval that the free cefepime concentration remained above the MIC of 8 mg/liter in 12 febrile neutropenic patients with hematological malignancy receiving 2-g i.v. q8h dosing. The whiskers extend to 1.5 times the interquartile range from Q1 or Q3 or the highest/lowest point within the range. The black and gray areas represent the distances from the 1st quartile to the median and from the median to the 3rd quartile, respectively.

(BMI)/obesity observed in our cohort (Table 1) (16, 30, 31). On the other hand, previous estimates of total clearance and half-life in healthy volunteers (21) (8.4 liters/h for 2.3 h) and critically ill burn patients (28) ($\approx$ 9 liters/h for 2.45 h) are comparable with this study (8.7 liters/h for 2.5 h). Given that cefepime is predominantly eliminated unchanged via glomerular filtration (21), the similarities to healthy individuals' data are sensible as all patients in this study exhibited normal renal function (Table 1). However, augmented renal clearance is not uncommon in febrile neutropenic patients with normal renal function; therefore, higher than usual clearance of cefepime is a possibility in such cases (32).

Considering the conservative PK/PD target of 60% $fT_{>MIC}$, unbound cefepime concentrations were greater than the highest anticipated MIC of susceptible organisms (8 mg/liter) for all patients in this study. The median free concentration at 60% of the dosing interval was 17 mg/liter, a value greater than 4 $\times$ the MIC of cefepime for the majority of organisms, including many *P. aeruginosa* clinical isolates for which cefepime MIC values may be $\leq$ 4 mg/liter (29). For β -lactam antibiotics, including cefepime, maximal bacterial killing is expected to occur at concentrations of about 4 to 5 $\times$ the MIC (33). However, a more pragmatic PK/PD target for β -lactam antibiotics in immunocompromised neutropenic patients may be 100% $fT_{>MIC}$, which was attained in 55% of the dosing intervals assessed in this study, when considering the empirical MIC breakpoint of 8 mg/liter. The median unbound trough cefepime concentrations were just below or above 8 mg/liter for three consecutive days at steady state (Fig. 2) and were consistent with previous findings in critically ill patients (27).

Therefore, if considering PK/PD targets, a high-dose cefepime regimen (2 g i.v. q8h) appears to be adequate for the majority of patients and organisms. This dose provided 100% $fT_{>MIC}$ coverage for 94% of the dosing intervals in this study for organisms with MIC breakpoints of $\leq$ 4 mg/liter. The high-dose regimen is also supported by previous studies with less frequent dosing schedules (2 g i.v. every 12 h [q12h]) that have shown that trough concentrations can be low for the majority of febrile neutropenic patients (17). Similar findings in critically ill patients suggest that such low dosing regimens are inadequate when considering empirical therapy against less susceptible Gram-negative organisms (27, 34). Median trough concentrations in this study were also marginally close to the 8-mg/liter breakpoint (Fig. 2), suggesting that de-escalation from the current high-dose therapy may result in suboptimal exposure in patients with normal renal function.

Since most organisms have a relatively low MIC breakpoint for cefepime (MIC of $\leq$ 2), with the exception of few Gram-negative isolates (e.g., *P. aeruginosa*) (25), the trough concentrations achieved in this study (Fig. 2) will also meet a more aggressive PK/PD target of 100% $fT_{>4\times MIC}$ for most patients. A 100% $fT_{>4\times MIC}$ has been recommended for cefepime in order to maximize microbiological success in treatment of Gram-negative infections (33). However, this may require high trough concentrations for pseudomonal infections ($>$ 32 mg/liter), risking toxicity. Lamoth et al. (35) previously suggested that the threshold for cefepime-induced neurotoxicity, including those other than seizure, may be as low as 15 to 20 mg/liter (total concentration), although convulsive seizures are more likely to occur at concentrations of about 70 mg/liter or higher (36). Six out of 31 trough concentrations in this study (19%) fall within the 15- to 20-mg/liter range, although no neurological toxicities were observed. Given high variability in concentrations

(the coefficient of variation of trough concentrations was about 50% in this study), the high-dose therapy is likely to result in concentrations beyond these "low thresholds" even in patients with normal renal function. Indeed there are some case reports of neurotoxicity in patients with normal renal function (37, 38). If the aforementioned thresholds can be validated in large trials, the range from empirical coverage to "toxicity" (trough concentrations of 8 to 20 mg/liter) would amount to a narrow therapeutic index warranting regular therapeutic drug monitoring (TDM).

The high-dose regimen (2 g i.v. q8h) was used in most of the published comparative clinical trials with adult febrile neutropenic patients (about 60%) included in the meta-analyses that initially suggested increased mortality with cefepime therapy; while low-dose regimens (1 to 2 g twice daily) were used in the rest (5, 6). Whereas studies that monitored cefepime concentrations from the low-dose regimens (17, 27, 34) suggest that underexposure is likely, measured concentrations from this and other studies (27) of the high-dose therapy indicate that this may occur only if high-MIC organisms are involved. Given the sample size limitation of this study, more data from large trials may be necessary to exclusively rule out underexposure against usually susceptible organisms in the presence of variable and continually changing susceptibility to current antibiotics. In addition to this, for some special population groups, such as those with high creatinine clearance and obesity, concentrations are likely to be far below the empirical breakpoints. The lowest unbound trough concentrations among our patients were observed for the participant with high creatinine clearance (2 mg/liter for P12) and those with marked obesity (3 mg/liter for P10 and P11) (Table 1 and Fig. 2). In such patients, extended infusion over half of the dosing interval may significantly improve the probability of target attainment without increasing the total dose administered, thus minimizing the apparent toxicity concerns (15, 39). Clinical studies have reported increased percentage of $fT_{>MIC}$ with prolonged infusion for cefepime (39, 40) and other β -lactam antibiotics (15, 41). Current PK/PD understanding is that improved exposure can potentially translate into improved clinical outcome. In support of this, a retrospective study by Bauer et al. (42) reported a mortality benefit from the use of an extended-infusion cefepime regimen. However, a recent systematic review by Burgess et al. (43) suggests that, despite the accumulating evidence of improved PK/PD target attainment, the correlation of this with optimal clinical outcome is yet to be demonstrated in a well-designed randomized prospective study, given the methodological limitations of existing studies.

A similar limitation of this study is that no outcome assessment was performed to describe if achievement of adequate PK/PD exposure was associated with favorable patient outcomes. It was not possible to perform any preliminary assessment because of the small sample size and also the variability in the type and schedule of concomitant antibiotic therapy (gentamicin for 1 to 3 days or vancomycin). In addition, 4 out of 12 patients did not complete cefepime therapy due to persisting fever. Even though this observation does not allow any conclusion (small sample size), a recent study also reported clinical failure with cefepime therapy despite achievement of 100% $fT_{>MIC}$ (44). In addition to this, a previous study has challenged the ability of existing cefepime breakpoints to predict clinical outcomes (45). Taken altogether, there seems to be accumulating evidence suggesting a need for critical reevalua-

tion of PK/PD properties of cefepime to confirm if the current dosing targets correlate with optimal clinical outcomes.

Conclusions. A high-dose cefepime regimen (2 g i.v. q8h) appears to provide appropriate antibiotic exposure in febrile neutropenic patients with normal renal function given that the MIC of the anticipated organisms is ≤ 4 mg/liter. However, based on current PK/PD recommendations, it may frequently fail to achieve maximum targets against higher MIC Gram-negative organisms. Plasma drug concentrations are highly variable among patients, suggesting that, in the absence of a well-defined therapeutic range and common toxicity/treatment failure concerns, monitoring of the cefepime concentration would be advantageous to support rational clinical decisions. The correlation of current PK/PD recommendations with favorable patient outcomes deserves ongoing thorough clinical investigation.

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We declare none of the authors have competing interests.

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