Altered Pharmacokinetics of Piperacillin in Febrile Neutropenic Patients with Hematological Malignancy

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This study assessed the pharmacokinetics and dosing adequacy of piperacillin in febrile neutropenic patients after the first dose. Pharmacokinetic analysis was performed using noncompartmental methods. We observed an elevated volume of distribution (29.7 ± 8.0 liters [mean ± standard deviation]) and clearance (20.2 ± 7.5 liters/h) compared to data from other patient populations. Antibiotic exposure did not consistently result in therapeutic targets. We conclude that alternative dosing strategies guided by therapeutic drug monitoring may be required to optimize exposure.

Febrile neutropenia is a medical emergency associated with high mortality (1). The immediate administration of broad-spectrum antibiotics is crucial for reducing the risk of mortality (2). β-lactam antibiotics active against Pseudomonas aeruginosa, such as piperacillin-tazobactam, are common first-line empirical agents used to treat this condition. Emerging data suggest that the standard dosing regimens for these antibiotics may not provide adequate exposure due to pharmacokinetic (PK) alterations emanating from pathophysiological processes associated with neutropenia (3, 4). More specifically, the proportion of the dosing interval in which the free-drug concentration remains above the MIC ($T_{f/MIC}$) may be diminished. For β-lactams, $T_{f/MIC}$ is the pharmacokinetic-pharmacodynamic (PK-PD) index that best correlates with clinical outcome (5).

Most of the evidence for the altered β-lactam PK and associated poor PK-PD target attainment in febrile neutropenic patients is available for other antibiotics, such as ceftazidime (6) and meropenem (7). The data are meager for piperacillin in this regard, even though it is commonly considered the preferred β-lactam for febrile neutropenia. To our knowledge, there is no well-described recent study except the works of Drusano et al. (8, 9), which reported no PK alterations in febrile neutropenic patients, a finding which is contrary to the recent reports of PK alterations and variability across many antibiotic classes (3, 4). Therefore, the aims of this study were to describe the PK of piperacillin in patients with febrile neutropenia following chemotherapy for hematological malignancy and to assess the adequacy of the standard initial dosing to attain the recommended pharmacodynamic (PD) target against all possible organisms during the first dosing interval.

Twelve patients ≥18 years of age with hematological malignancies were enrolled when prescribed piperacillin-tazobactam after developing febrile neutropenia. Febrile neutropenia was defined as the presence of a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) for >1 h, with either a neutrophil count of <500 cells/mm³ or a count of <1,000 cells/mm³ with a predicted decrease to <500 cells/mm³ (2). Patients were excluded if they had a known/suspected allergy to β-lactams, marked renal failure (defined as a glomerular filtration rate [GFR] of <20 ml/min) or hepatic impairment (transaminases > 500 U/liter) or were pregnant. Ethics approval for the study was granted by the human research ethics committees of The Queen Elizabeth Hospital (HREC/12/TQEMLMH/157) and the University of South Australia (application no. 000031077). All patients received 4.5 g piperacillin-tazobactam every 8 h via intravenous bolus infusion over 30 min, followed by 15 to 20 min of line flushing. In addition, all patients received a single 7-mg/kg of body weight dose of gentamicin.

Serial blood samples were collected just prior to the first dose, at the end of line flushing, and at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, and 7 h after the start of infusion, and then a final sample was collected just before the second dose. The total plasma concentrations of piperacillin were quantified using a validated liquid chromatography tandem mass spectrometry method. Non-compartmental pharmacokinetic analysis was performed using PKSolver (10). The $T_{f/MIC}$ was estimated after the first dose from the log-linear elimination phase. First, the terminal elimination constant ($k_d$) was estimated with the PKSolver software (10). Next, considering 30% protein binding for piperacillin (11), the $T_{f/MIC}$ was calculated for P. aeruginosa and Enterobacteriaceae based on the breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (12) and the Clinical and Laboratory Standards Institute (CLSI) (13). As this study aims to assess the adequacy of the initial dosing against all possible organisms, we selected P. aeruginosa and Enterobacteriaceae, which have the highest MIC breakpoints according to interpretative criteria of the EUCAST and CLSI.

Received 20 January 2014 Returned for modification 11 February 2014 Accepted 22 March 2014 Published ahead of print 31 March 2014 Address correspondence to Fekade Bruck Sime, fekade.sime@mymail.unisa.edu.au. Copyright © 2014, American Society for Microbiology. All Rights Reserved. doi:10.1128/AAC.02340-14
The demographic characteristics of the study participants are given in Table 1. All patients were febrile and neutropenic, with cell counts too low to perform differential counts. Blood cultures were positive for infection in four patients (patients 1, 3, 9, and 10), and the organisms isolated were organisms resembling staphylococci, *Enterobacter aerogenes*, *P. aeruginosa*, and *Escherichia coli*, respectively. The plasma concentration-time profile for total piperacillin concentration after a single dose of 4.5 g piperacillin-tazobactam is depicted in Fig. 1. Pharmacokinetic parameter estimates of the individual study participants are given in Table 2.

We observed an elevated volume of distribution (V) (29.7 ± 8.0 liters [mean ± standard deviation]) and clearance (CL) (20.2 ± 7.5 liters/h) for the cohort in this study. Different factors may contribute to the expansion of the V. One important factor is the alteration of capillary permeability and subsequent extravasation of vascular fluid during infection, which is mediated by various factors (14). The increase might also occur due to hypoalbuminemia, which is common in hematological malignancies and was observed for all participants in this study (Table 1). Low albumin concentrations reduce plasma oncotic pressure, subsequently leading to enhanced fluid extravasation. However, the effect of hypoalbuminemia is most prominent for highly protein-bound antibiotics and therefore might have limited contribution toward the increased piperacillin V observed in this study (30% protein binding) (4, 15). Changes in the glomerular filtration rate (GFR) have been implicated in the variability of antibiotic CL in febrile patients with hematological malignancies (6). A very high GFR value is common in patients undergoing chemotherapy (16) and may contribute to elevated CL. Serum creatinine clearance (determined using the Cockcroft-Gault formula) was also distinctively high for some participants (Table 1, patients 8 to 12), indicating the presence of augmented renal clearance contributing to the significant increase in individual piperacillin clearances (Table 2).

### TABLE 1 Characteristics of the study participants

<table>
<thead>
<tr>
<th>Patient no. or summary data</th>
<th>Hematological malignancy</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Body wt (kg)</th>
<th>Ht (cm)</th>
<th>Serum creatinine (µmol/liter)</th>
<th>Creatinine clearance^b</th>
<th>Albumin (g/liter)</th>
<th>Liver enzymes^c (U/liter)</th>
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<td>27</td>
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<td>79</td>
<td>69</td>
<td>173</td>
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<td>51.4</td>
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Median (interquartile range) 64.5 (60.5–71.0)  75.0 (63.7–93.2)  173.5 (169.2–176.7)  66.5 (60.0–72.0)  76.1 (64.7–100.1)  27.5 (26.0–30.2)  26 (15.5–40.2)  21.0 (14.7–25.0)

^a M, male; F, female.

^b Using the Cockcroft-Gault formula.

^c ALT, alanine aminotransferase; AST, aspartate transaminase.

FIG 1 Plasma concentration-time profile for total piperacillin concentration after a single dose of 4.5 g piperacillin-tazobactam in 12 febrile neutropenic patients with hematological malignancies.
Median hyperdynamic cardiovascular state (e.g., septic patients due to increased renal blood flow secondary to a febrile patients might occur in a way similar to that in critically ill patients when 100% fT MIC was considered as a target. There is an emerging understanding that neutropenic patients may require a higher PK-PD index for a successful outcome due to their compromised immune response. Ariano et al. (21), for instance, showed that for meropenem, an 80% clinical response is observed when fT MIC is >75%, a value much higher than the conventional 40% fT MIC. Similarly, for piperacillin and cephalosporins, which lack postantibiotic effect against Gram-negative organisms, previous data from some animal studies have indicated that in the settings of profound neutropenia, free concentrations should be greater than the MIC for 90% to 100% of the dosing interval to ensure efficacy (22). This is well supported by studies that demonstrate the profound effect of host immunity on PD parameters (23–25). In immunocompromised hosts, a more aggressive antibiotic action through increased antibiotic exposure time may be required to achieve the same response as in immunocompetent hosts.

Considering 100% fT MIC, our results indicate that the standard bolus dose of 4.5 g piperacillin-tazobactam every 8 h is unlikely to provide optimal exposure against P. aeruginosa and Enterobacteriaceae (Fig. 2). Optimal exposure should be achieved as early as possible to reduce the risk of mortality (26). In the current study, concentrations remained below the MIC of P. aeruginosa for about 5 to 6 h of the first dose interval. Such extended subinhibitory exposure should be avoided to reduce the risk of selecting resistant organisms (27).

We believe that the present intermittent dosing regimen should be reviewed and replaced with new dosing strategies that ensure adequate antibiotic exposure and reduce the risk of the emergence of antibiotic resistance. Better exposure can be achieved with more frequent administration of the dose (e.g., 4.5 g every 6 h), which in effect increases the total daily dose.

TABLE 2 Pharmacokinetic parameter estimates of piperacillin after a single dose of 4.5 g piperacillin-tazobactam in 12 febrile neutropenic patients with hematological malignancies

In fact, drug exposure was moderately correlated with creatinine clearance (r = −0.663, P < 0.05). Augmented renal clearance in febrile patients might occur in a way similar to that in critically ill septic patients due to increased renal blood flow secondary to a hyperdynamic cardiovascular state (17). However, in hyperdynamic patients in whom there is no stable creatinine concentration, predictive equations of creatinine clearance and GFR are likely to be incorrect in assessing the rapidly changing renal function and, hence, antibiotic CL (18, 19).

The elevated CL and significant expansion of the V in our patients explain the very low observed trough concentrations (median, 0.5 mg/liter). This is far below the clinical susceptibility breakpoint of expected pathogens, such as Enterobacteriaceae (8 mg/liter for EUCAST and 16 mg/liter for CLSI) and P. aeruginosa (16 mg/liter for CLSI and EUCAST) (12, 13). The fT MIC achieved for P. aeruginosa after the first dose (Fig. 2) was suboptimal compared to the conventionally recommended PD targets of about 50% to 60% fT MIC (20). Similarly, for Enterobacteriaceae, the fT MIC was suboptimal for the majority of participants when conventional PD targets were considered and in all patients when 100% fT MIC was considered as a target. There is an emerging understanding that neutropenic patients may require a higher PK-PD index for a successful outcome due to their compromised immune response. Ariano et al. (21), for instance, showed that for meropenem, an 80% clinical response is observed when the fT MIC is >75%, a value much higher than the conventional 40% fT MIC. Similarly, for piperacillin and cephalosporins, which lack postantibiotic effect against Gram-negative organisms, previous data from some animal studies have indicated that in the settings of profound neutropenia, free concentrations should be greater than the MIC for 90% to 100% of the dosing interval to ensure efficacy (22). This is well supported by studies that demonstrate the profound effect of host immunity on PD parameters (23–25). In immunocompromised hosts, a more aggressive antibiotic action through increased antibiotic exposure time may be required to achieve the same response as in immunocompetent hosts.

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The mode of administration used (i.e., 30-min bolus infusion) could also be optimized. The use of extended infusion (EI) or continuous infusion (CI) is an attractive approach to maximize the $fT_{>MIC}$ without increasing the total daily dose (28). In combination with a loading dose, EI or CI can be used to avoid the initial suboptimal exposure observed with the intermittent schedule in this study. CI may be practically challenging, as it requires a dedicated intravenous (i.v.) line, which may not be available given that patients often receive a number of other drugs and perhaps nutritional support. EI is more practical in this regard, allowing sufficient line access for other purposes. Another challenge is that a fixed EI or CI regimen may not reach the PD target consistently in all patients due to the variability in CL and V. Dose individualization through therapeutic-drug monitoring (TDM) may be useful to ensure optimal exposure in every patient.

Often, culture results are not available initially for use in TDM. We therefore suggest initial dosing aimed at organisms with high MICs, such as *P. aeruginosa*, and then dosing can be readjusted based on the specific organism MIC. Local institutional antibiograms should be utilized whenever available, as there is geographical and institution-to-institution variability in susceptibility. However, in the absence of such data, EUCAST/CLSI breakpoints provide reasonable references for use in TDM. This has been well demonstrated for piperacillin (and other β-lactam antibiotics) in critically ill patients who exhibit PK alterations similar to those observed in this study (29). However, it has not yet been described in febrile neutropenic patients. Further clinical studies are required to assess the utility of TDM of piperacillin in febrile neutropenic patients.

In conclusion, the observed high V and CL suggest altered PK of piperacillin in febrile neutropenic patients. Standard intermittent dosing of 4.5 g piperacillin-tazobactam (i.v. bolus, every 8 h) resulted in suboptimal antibiotic exposure and therefore was not sufficient. We recommend TDM-guided optimization with EI or adjusted dosing frequency to ensure exposure to inhibitory concentrations for the entire dosing interval.

ACKNOWLEDGMENT

We declare no competing interests.

REFERENCES


