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Original Article

Evaluation of pharmacokinetic/pharmacodynamic and clinical outcomes with 6-hourly empiric piperacillin-tazobactam dosing in hematological malignancy patients with febrile neutropenia☆

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ABSTRACT

Background: Piperacillin-tazobactam is commonly used in neutropenic sepsis at standard doses that do not account for inter-individual differences in age, bodyweight and renal function. This study was designed to assess the rate of attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets in patients receiving piperacillin/tazobactam therapy and to evaluate the effect on clinical outcomes.

Methods: Patients undergoing intensive chemotherapy for aggressive hematological malignancies were enrolled and treated with piperacillin/tazobactam 4 g/0.5 g every 6 h as initial antimicrobial therapy for first fever. Plasma drug concentrations were assayed at 50% and 100% of the dosing interval and compared with target MIC breakpoint of 16 mg/L to calculate the primary endpoints of 50% and 100% time above MIC (fT > MIC), respectively. Secondary endpoints included time to clinical cure, length of hospital stay, duration of antibiotics, and clinical treatment success.

Results: Fifty-eight percent (14/24) of patients achieved 50% fT > MIC while only 4% (1/24) achieved 100% fT > MIC. Higher creatinine clearance was significantly associated with lower trough drug concentration and appeared to be the dominant reason for the poor PK/PD target attainment. Median time to clinical cure, duration of antibiotic therapy, and hospital length of stay was 3, 13 and 21 days, respectively. There were no statistically significant differences in these outcomes between patients who did and did not achieve 100% fT > MIC.

Conclusions: A significant majority of febrile neutropenic patients fail to achieve PK/PD targets with 6-hourly piperacillin dosing, although the clinical implications of this finding are unclear. Larger studies are needed to assess any impact on morbidity and mortality.

This trial is registered on the ANZCTR (ACTRN12618000110280).

1. Introduction

Bacterial sepsis occurring as a complication of chemotherapy-induced neutropenia is a major cause of hospitalisation and mortality in patients with hematological malignancies [1]. Monotherapy with anti-Pseudomonal beta-lactam agents, such as piperacillin-tazobactam, is widely recommended for empiric treatment [2,3]. These agents exhibit a time-dependent mechanism of action for which the degree of antimicrobial efficacy depends on the length of

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time that the drug concentration exceeds the minimum inhibitory concentration of the target pathogen [4]. A convenient measure of this pharmacokinetic/pharmacodynamic (PK/PD) property is the proportion of the dosing interval in which the plasma free drug concentration remains above the target minimum inhibitory concentration (fT > MIC), with a minimum proportion of 50% (or even 100%) considered essential in severely unwell patients [5].

The pharmacokinetic properties of beta-lactam antibiotics are affected by the physiologic changes that occur in sepsis. Data from the critical care patient population show that increased renal drug clearance, increased volume of distribution and altered protein binding frequently occur, leading to subtherapeutic antibiotic concentrations which are also associated with negative clinical outcomes [6,7]. Similar alterations in beta-lactam pharmacokinetics have been described in neutropenic patients with sepsis [8,9]. Several small studies have shown that fixed-dose piperacillin regimens (co-administered with tazobactam, 4.5 g 8-hourly) produce poor PK/PD target attainment and may therefore be inappropriate for this highly vulnerable population [10,11]. However, definitive evidence of a relationship between subtherapeutic fT > MIC and inferior clinical outcomes has yet to be demonstrated.

The primary objective of this prospective cohort study was to evaluate the fT > MIC with 6-hourly piperacillin-tazobactam dosing in a cohort of hematology patients with chemotherapy-induced febrile neutropenia. The secondary objectives were to assess the alterations in creatinine clearance with onset of sepsis in neutropenic patients and the impact of PK/PD target attainment on clinical outcomes including treatment success, duration of antibiotic treatment and hospital length of stay.

2. Patients and methods

The study was conducted in the Hematology and Bone Marrow Transplant Unit at the Royal Brisbane and Women's Hospital in Brisbane, Australia. This is a 48-bed tertiary level Hematology service with intensive care and clinical infectious diseases support. The study protocol and all study procedures were approved by the RBWH Human Research Ethics Committee prior to subject enrolment (RBWH HREC/15/QRBW/104). The trial was retrospectively registered with the ANZCTR (ACTRN12618000110280).

2.1. Enrolment criteria

Patients aged ≥18 years with aggressive hematological malignancies undergoing inpatient chemotherapy with anticipated duration of neutropenia (absolute neutrophil count $<1 \times 10^9$/L) of more than 7 days were eligible to participate. Patients with documented hypersensitivity to penicillin, pre-existing renal impairment (eGFR <60 ml/min), or pregnancy were excluded.

2.2. Study procedures

Eligible patients provided written consent at the time of chemotherapy commencement. Baseline demographic and disease data, and 24-h urine collection for creatinine clearance calculation were collected at enrolment. Blood samples for piperacillin concentration were collected at the time of first fever as described below. Repeat 24-h urine collection for creatinine clearance was performed on the day following onset of first fever, commencing after the first morning urine void. Serum and urine creatinine concentrations were measured using the Beckman Coulter Dxc800 analyser.

Measured creatinine clearance was calculated using the formula:

CrCl = (urine creatinine concentration, μmol/ml × urine volume, ml)/(plasma creatinine concentration, μmol/ml × time, min).

Body surface area (BSA) was calculated using the formula:

BSA = sqrt ((height, cm × weight, kg)/3600)

Creatinine clearance corrected for BSA was applied using the formula:

CrClcorr = CrCl × (1.73/BSA)

All participants were followed from the time of enrolment until discharge or death. Duration of intravenous antibiotic therapy was determined by culture results; in culture-negative cases, therapy was ceased on recovery of neutrophil count $\geq 1 \times 10^9$/L with resolution of fevers to <38 °C. Data collection included clinical and demographic data, antibiotic use, microbial culture results, treatment success and survival.

2.3. Blood sampling and drug assay

At the time of first fever >38 °C patients were commenced on 6-hourly piperacillin-tazobactam 4.5 g infused over 30 min as per unit protocol for febrile neutropenia. Within 24–48 h of first antibiotic dose, participants underwent peripheral blood sampling for serum free piperacillin concentration measurement at two timepoints: halfway through the dosing interval (50%) and at the end of the dosing interval immediately prior to the next due dose (100%). Unbound plasma piperacillin concentrations were determined using high-performance liquid chromatography as previously described [12].

2.4. Outcome definitions

The primary outcome was the proportion of patients who achieved the PK/PD targets of 50% fT > MIC and 100% fT > MIC, defined as free antibiotic level ≥ MIC at 50% and 100% of the dosing interval, respectively. The MIC for *Pseudomonas* spp. of 16 mg/L was used in accordance with EUCAST recommendations (http://www.eucast.org/clinical_breakpoints/).

Secondary outcomes included a) time to clinical cure, defined as number of days from first fever to normalisation of temperature, blood pressure and pulse rate, b) duration of antibiotic therapy, defined as number of days of intravenous antibiotic therapy, c) length of hospital stay from time of first fever, and d) clinical treatment failure, defined as requirement for change in antibiotic therapy due to persistent clinical signs of sepsis in the absence of resistant organism or medication intolerance.

2.5. Statistical analysis

Descriptive statistics were used for the primary outcome. Time-to-event outcomes including time to clinical cure and duration of antibiotics were analysed using Kaplan-Meier curves and log-rank test. The Student's t-test and chi-squared test were used for comparisons of continuous and categorical variables where appropriate. IBM SPSS Version 24.0 (SPSS Inc., Chicago IL, USA) was used for statistical analysis.

3. Results

3.1. Patient characteristics

Consecutive patients meeting inclusion/exclusion criteria were enrolled between August 2015 and February 2017. A total of 32

patients were enrolled, of whom 8 were excluded from analysis due to use of non-study antibiotic (n = 2), absence of fever during neutropenic period (n = 3) or incomplete data collection (n = 3).

The characteristics of the 24 patients who were included in the primary analysis are listed in Table 1. The median age was 59 years and 58% were males. The median body mass index was 26.3 kg/m^2. The primary diagnosis was acute leukaemia in 22/24 (92%). Median baseline corrected creatinine clearance was 108 ml/min/1.73 m^2. All patients were treated with piperacillin-tazobactam (piperacillin) 4 g/500 mg every 6 h delivered as a 30-min infusion. Nine patients (38%) received concurrent empiric vancomycin therapy. Antibiotic concentrations were collected within 24 h of the first dose in 17/24 (71%) patients, and between 24 and 48 h in 7/24 (29%) patients.

3.2. Attainment of PK/PD target

The median free piperacillin concentrations at 50% and 100% of the dosing interval were 19 mg/L (IQR 9.7–29.3 mg/L) and 2.25 mg/L (IQR 0.70–4.45 mg/L) respectively (Fig. 1). Using the recommended MIC susceptibility breakpoint of 16 mg/L for *Pseudomonas* spp., 14/24 (58%) patients achieved 50% fT > MIC and 1/24 (4%) achieved 100% fT > MIC. To explore the determinants of trough piperacillin concentration, linear regression analysis was performed using the independent variables of creatinine clearance, body mass index (BMI) and age. Creatinine clearance showed an inverse association with trough piperacillin level (regression coefficient −0.453 mg/L/ml/min, 95% CI [-0.082, −0.006], p = 0.026), while BMI and age showed no significant effect.

3.3. Measured creatinine clearance

Complete data was available for 25 febrile episodes in 24 patients. The mean corrected creatinine clearance was 117 ml/min/1.73 m^2 at timepoint 1 (study entry) and 120 ml/min/1.73 m^2 at timepoint 2 (within 24 h of first fever). The mean difference was not significant (2.88 ml/min/1.73 m^2, 95% CI [-7.69, 13.45], p = 0.58). As expected, lower creatinine clearance was associated with increasing age (regression coefficient −0.6 ml/min/year, p = 0.002).

3.4. Clinical outcomes

Median time to clinical cure, duration of antibiotic therapy, and hospital length of stay was 3, 13 and 21 days, respectively. No patients died during follow-up. Outcomes according to PK/PD target attainment are presented in Table 2. The time to clinical cure and duration of antibiotic therapy was longer in the patients who failed to attain 100%fT > MIC, however statistical significance could not be demonstrated as there was only one patient who attained this target. Using the less stringent PK/PD target of 50% fT > MIC, median time to clinical cure was the same in both groups (3 days), whereas length of antibiotic therapy and hospital length of stay were slightly longer in the patients who failed to attain this target; again, statistical significance could not be demonstrated.

After initial treatment with piperacillin, 14/24 patients (58%) required change in antibiotic therapy due to a) persistent sepsis of unknown source (designated as 'clinical treatment failure', n = 9), b) isolation of resistant organism (n = 3), or c) adverse reaction to piperacillin (n = 2). The remaining 10 patients experienced resolution of clinical signs of sepsis on piperacillin therapy and were therefore designated as 'clinical treatment success'. All of the patients who experienced clinical treatment failure had failed to achieve 100% fT > MIC and the majority (5/9, 56%) failed to achieve 50% fT > MIC. Conversely, half of the patients who failed to achieve 100% fT > MIC still experienced clinical treatment success (Table 3). The odds ratio for treatment failure according to attainment of 50% fT > MIC was 0.34 (95% CI [0.05, 2.26]; Fisher's exact p = 0.37).

Table 1
Patient characteristics.

Patient	Age	Gender	Diagnosis	BMI (kg/m^2)	Baseline CrCl (ml/min/1.73m^2)	Blood culture result	Susceptible to Piperacillin/Tazobactam?[a]	Clinical Treatment Success?
1	60	M	AML	25.62	94	Staphylococcus epidermidis	N (MR)	N (resistant organism)
2	63	M	AML	21.22	95	Dermabacter hominis	Y	N (persistent sepsis)
3	60	M	ALL	23.78	121	*Pseudomonas aeruginosa*	N (MIC>16)	N (resistant organism)
4	45	F	AML	32.66	142	NG	–	N (persistent sepsis)
5	59	F	ALL	32.47	82	*Klebsiella pneumoniae*	N (MIC>32)	N (resistant organism)
6	44	M	ALL	31.64	–	NG	–	Y
7	45	M	ALL	24.21	154	Streptococcus viridans group	Y	Y
8	34	F	AML	26.45	166	NG	–	N (adverse reaction)
9	35	F	AML	32.24	175	NG	–	N (persistent sepsis)
10	59	F	AML	25.43	120	NG	–	Y
11	71	M	ALL	29.67	–	*Pseudomonas aeruginosa*	Y	Y
12	24	M	NHL	26.79	119	*Escherichia coli*	Y	N (persistent sepsis)
13	66	M	AML	24.38	95	NG	–	Y
14	38	M	AML	26.22	128	NG	–	N (persistent sepsis)
15	62	F	AML	24.30	108	NG	–	Y
16	65	M	AML	25.47	93	*Escherichia coli*	Y	Y
17	67	M	AML	24.90	90	NG	–	N (adverse reaction)
18	39	M	AML	27.16	140	NG	–	N (persistent sepsis)
19	67	F	AML	27.64	85	NG	–	N (persistent sepsis)
20	40	F	AML	20.96	–	NG	–	Y
21	38	F	ALL	40.77	84	NG	–	N (persistent sepsis)
22	66	F	AML	37.74	94	NG	–	Y
23	63	M	AML	37.20	58	Staphylococcus epidermidis	N (MR)	Y
24	42	M	NHL	23.92	222	Staphylococcus epidermidis	N (MR)	N (persistent sepsis)

AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia; NHL = non-Hodgkin lymphoma; BMI = body mass index; CrCl = creatinine clearance; NG = no growth; MR = methicillin-resistant; MIC = minimum inhibitory concentration.
[a] Reported using VITEK 2 system (bioMérieux).

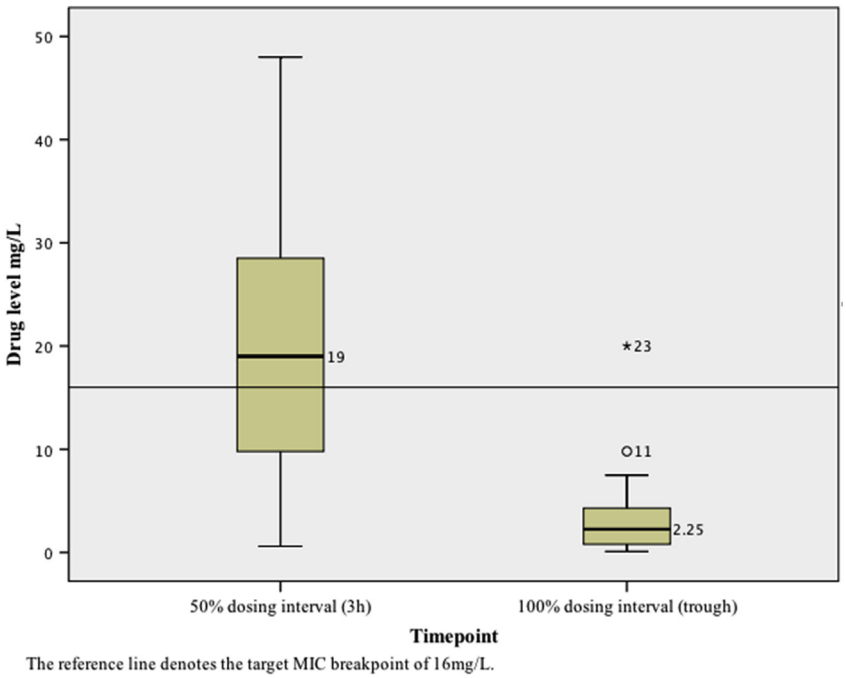

Fig. 1. Boxplot representing serum piperacillin concentrations at 50% and 100% of dosing interval.

Table 2
PK/PD target attainment and survival outcomes.

	100% fT > MIC		p-value	50% fT > MIC		p-value
	Yes n = 1	No n = 23		Yes n = 14	No n = 10	
Time to clinical cure (median, days)	1	3	0.12	3	3	0.26
Duration of IV antibiotics (median, days)	7	13	–	12	13	0.66
Length of stay (median, days)	25	21	0.89	20	21	0.83

4. Discussion

This single-site study prospectively examined the frequency of PK/PD target attainment with 6-hourly piperacillin dosing in hematology patients with febrile neutropenia. Despite the increased frequency of administration of the drug compared with the standard 8-hourly schedule, only 1/24 (4%) patients achieved the target of 100% fT > MIC using the recommended MIC breakpoint of 16 mg/L. Furthermore, only 14/24 (58%) achieved the less stringent target of 50% fT > MIC.

Our findings are consistent with published studies of other beta-lactam agents in the neutropenic patient population [8,10,13]. However, studies looking specifically at piperacillin in febrile neutropenia are uncommon. In a study of 56 oncology patients treated with piperacillin/tazobactam 4 g/0.5 g every 8 h, Rachow et al. found that the majority failed to achieve the PK/PD targets of 50% fT > 4xMIC or 100% fT > MIC using an MIC breakpoint of 16 mg/L [11]. The median piperacillin level at 4 h was 46.2 mg/L, significantly higher than the median mid-dosing interval level of 19 mg/L in our study; this is likely a reflection of the higher median age (66 years) and lower baseline renal function (median eGFR = 87 ml/min) in their cohort. Interestingly, subgroup analysis showed that patients with leukaemia were most likely to have low piperacillin concentrations compared with lymphoma and solid organ malignancies, possibly reflecting a more severe inflammatory response in the setting of profound neutropenia induced by anti-leukaemia therapy.

Table 3
PK/PD target attainment and clinical treatment outcome.

	100% fT > MIC		OR	50% fT > MIC		OR
	Yes	No		Yes	No	
Clinical treatment failure	0	9	–	4	5	0.34 (95% CI 0.05–2.26)
Clinical treatment success	1	9	–	7	3	

We acknowledge that the optimal PK/PD target for patients with febrile neutropenia has yet to be established. The evidence supporting various proposed PK/PD cutoffs for beta-lactam agents has been recently reviewed by Dellatre et al. [14]. In general, based on animal models and *in vitro* human samples, piperacillin targets of 100% fT > 4-6xMIC are believed to achieve maximal bacterial killing and to prevent bacterial regrowth and antibiotic resistance. Less aggressive targets of 50% fT > MIC are supported by various animal and *in vitro* models as being sufficient for bacterial killing. However, the higher concentrations (100% fT > 4-6xMIC) are difficult to achieve within an appropriately short timeframe in clinical practice with Monte Carlo simulations showing that only 7% of patients attain a serum concentration at this level after a single first dose of piperacillin [14]. Our choice of 100% and 50% fT > MIC in this study was felt to better reflect 'real-life' practice and is in line with previous work showing these targets to be clinically meaningful [7].

Likewise, our use of the MIC breakpoint of 16 mg/L is in line with international recommendations that empiric antibiotic selection is based on effective anti-Pseudomonal coverage. In clinical practice, identification of a pathogenic organism may take 24–48 h with further delay for individual MIC testing. Based on evidence that time to initiation of antibiotic therapy is the most critical determinant of outcome in sepsis, broad-spectrum cover is critical in this early period until therapy can be de-escalated according to culture results [15,16]. In our study, 2/24 patients had confirmed *Pseudomonas* sp. bloodstream infection, with other enteric Gram negative organisms found in a further 3/24 patients. In light of this, we found that even by lowering the target MIC breakpoint to 8 mg/L (recommended by EUCAST for Enterobacteriaceae), only one additional patient would have achieved the 100% fT > MIC target.

We hypothesise from our data that suboptimal piperacillin PK/PD performance in the neutropenic sepsis population is primarily attributable to accelerated renal drug clearance. Piperacillin is water-soluble, exhibits only modest protein binding and is 80% renally excreted, so that the plasma concentration is primarily determined by a) the size of the delivered dose and b) rate of renal elimination. In this study the daily dose of piperacillin was fixed at 16 g, but the baseline mean creatinine clearance was relatively high at 117 ml/min/1.73 m^2 and did not appear to increase further with the onset of sepsis. Since the majority of patients were undergoing induction chemotherapy for acute leukaemia, this high baseline creatinine clearance likely reflects the common use of aggressive intravenous hydration for tumour lysis prophylaxis. Inflammatory mediator-driven alterations in renal perfusion as a consequence of the acute leukaemia disease state may also play a role in augmenting renal clearance in these patients. Our data showed that higher creatinine clearance was significantly associated with lower trough piperacillin levels, whereas no relationship was found with body mass index or body surface area, suggesting that changes in volume of distribution may be of secondary importance.

Strategies that have been reported to improve PK/PD target achievement include shortening of the dose interval and/or the use of prolonged or continuous infusion times, with the latter approach associated with reduced hospital mortality in the general ICU population [17,18]. It has been demonstrated that 100% fT > MIC can be achieved in virtually all patients using continuous infusion piperacillin, despite high inter-individual variation in serum concentrations over the administration period [19]. Sime et al. showed that decreasing the dose interval of piperacillin to 6 h and extending infusion time to 3 h resulted in a significant improvement in the proportion of patients achieving 100% fT > MIC from 19% to 73%, using therapeutic drug monitoring to identify patients at risk of subtherapeutic dosing [20]. Despite this, an improvement in duration of fever and time to recovery from neutropenia could not be demonstrated due to small sample size as well as concomitant gentamicin therapy in the majority of patients.

Similarly, whilst the rates of PK/PD target attainment in our study were low, a negative impact on clinical outcomes was unable to be demonstrated. This may be due to the small sample size which is a significant limitation of this study. It is also likely that factors other than plasma antibiotic concentration contribute to outcomes in febrile neutropenia including polymicrobial infection, non-infective causes for fever, and the extent of drug distribution into various tissue compartments. The 30-day mortality rate in our study was zero, reflecting the rapid protocol-based escalation of antibiotic therapy in hospitalised neutropenic patients, and relatively low rates of multiresistant organisms in our population.

5. Conclusion

In this cohort of adult patients undergoing intensive chemotherapy for aggressive hematological malignancies, a 6-hourly piperacillin dose schedule was inadequate for target PK/PD target attainment in the majority of patients. A major determinant of this finding appears to be high rates of augmented renal drug clearance that is present *prior* to the onset of neutropenic sepsis. The study was underpowered to detect an impact on clinical outcomes including time to clinical cure, duration of antibiotics, length of hospital stay, or clinical treatment success. Further research is needed to establish whether alternative dosing strategies that may account for inter-individual differences in body weight or drug handling can improve clinically relevant outcomes in hematology patients with febrile neutropenia.

Conflicts of interest

None.

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