ORIGINAL ARTICLE

Optimizing Antibiotic Dosing: A Prospective Observational Study of Piperacillin/Tazobactam Plasma Levels in Critically Ill Patients with Augmented Renal Clearance

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ABSTRACT

INTRODUCTION: Managing antibiotic dosing in critically ill patients presents challenges especially in achieving optimal therapeutic levels. Thus, we conducted a study to evaluate how augmented renal clearance (ARC) affects the attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets in patients receiving piperacillin/tazobactam (PTZ) via continuous infusion. **MATERIALS AND METHODS:** A single-centred, prospective, observational study was conducted in intensive care unit at Sultan Ahmad Shah Medical Center @IIUM, Kuantan Pahang. A total of 43 adult patients with normal renal function treated as sepsis with standard PTZ doses via continuous infusion were included for the study and their blood were sampled for assessment of drug concentrations and PK/PD target attainment. **RESULTS:** There was substantial PK variability with 60% diagnosed with ARC and 37.2% of experienced piperacillin underexposure in which patients with ARC had significantly higher rates of underexposure at both distribution and steady-state phases. **CONCLUSION:** The high prevalence of ARC in these patients impacted the therapeutic PTZ levels and as many patients did not reach desired drug concentrations, there is increased risk of treatment failure without dose adjustment. These findings underscore the importance of individualized dosing strategies, particularly in critically ill patients with ARC, to optimize antibiotic therapy efficacy and mitigate the risk of inadequate treatment.

Keywords
augmented renal clearance, critically ill, piperacillin-tazobactam, subtherapeutic

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INTRODUCTION

Critically ill patients with augmented renal clearance often pose a formidable challenge in determining appropriate drug dosages to achieve optimal therapeutic efficacy. Augmented renal clearance (ARC) which is characterized by enhanced renal function and increased clearance of renally eliminated drugs is a common phenomenon observed in critically ill patients.[1-3] The dynamic nature of ARC complicates the attainment of target drug concentrations particularly for antibiotics like Piperacillin/Tazobactam (PTZ) which are predominantly excreted renally.

In recent years, pharmacokinetic studies have emerged as invaluable tools in understanding the disposition of drugs in critically ill patients especially those with altered renal function. Many studies have provided critical insights into the pharmacokinetic parameters governing drug disposition, absorption, distribution, metabolism, and elimination in this patient population.[4-7] By quantifying plasma concentrations of drugs like PTZ, pharmacokinetic studies have facilitated the optimization of dosing regimens, thereby improving therapeutic outcomes, and minimizing the risk of treatment failure or adverse events.

Piperacillin/Tazobactam is a broad-spectrum β-lactam antibiotic combination that is commonly used in the management of severe infections including pneumonia,

sepsis, intra-abdominal infections, and in critically ill patients. However, the pharmacokinetics of PTZ can be significantly altered in the presence of ARC/ leading to suboptimal drug exposure and potentially compromising treatment efficacy.[8-10] Consequently, understanding the impact of ARC on PTZ pharmacokinetics is crucial for tailoring dosing strategies and ensuring therapeutic success in this vulnerable patient population.

Pharmacokinetic studies evaluating PTZ plasma concentrations in critically ill patients with ARC have provided valuable insights into the factors influencing drug disposition and the challenges associated with achieving target drug levels.[10-14] Studies have highlighted the importance of considering patient-specific factors such as renal function, body weight, and severity of illness, in dose individualization and therapeutic drug monitoring.[12-14]

Pharmacokinetic modelling and simulation techniques have been instrumental in predicting drug exposure and guiding dose adjustments in patients with ARC. By integrating pharmacokinetic data with clinical parameters, these modelling approaches enable clinicians to optimize dosing regimens and achieve target drug concentrations while minimizing the risk of toxicity or treatment failure.[12]

Despite the advancements in pharmacokinetic research, several knowledge gaps persist regarding the optimal management of PTZ therapy in critically ill patients with ARC. Limited data are available on the impact of ARC on PTZ pharmacokinetics in specific patient populations such as those with varying degrees of renal dysfunction or concomitant organ dysfunction. Additionally, the clinical implications of subtherapeutic drug concentrations and the potential strategies for dose optimization remain areas of active investigation.

In view of all these considerations, our study was conducted to explore the assessment of PTZ plasma concentration in critically ill patients with ARC, emphasizing the importance of pharmacokinetic parameters in guiding precise dosing strategies. By synthesizing existing evidence and highlighting key research findings, our study aimed to underscore the significance of pharmacokinetic studies in optimizing PTZ therapy and improving clinical outcomes in critically ill patients with ARC.

MATERIALS AND METHODS

This study which was a single-centre, prospective observational study design had been approved by the medical ethical committee of the the International Islamic University Malaysia (IREC 2020-110, 29 March 2021).

SUBJECT

All patients who were admitted to the intensive care unit (ICU) at Sultan Ahmad Shah Medical Centre (SASMEC) @ IIUM during the study period were screened for the study. Patients who fulfilled the inclusion and exclusion criteria were recruited after informed consents were obtained. The inclusion criteria were patient age 18 years old or more with serum creatinine <120μmol/L, ICU stay >24hours and received continuous infusion of PTZ for a sepsis. The exclusion criteria were pregnant and lactating mother, history of allergy to β-Lactam antibiotics, was having an acute kidney injury (AKI) according to KDIGO criteria, underlying chronic kidney disease (CKD), and receiving diuretics during the screening period.

ANTIBIOTIC ADMINISTRATION

Selected patients were administered a loading dose of 4.5g PTZ over 30min, followed by continuous infusion 4.5g Q6hr (16g/2g in 24 hours). The syringe was changed every 8 h using a syringe pump through a central venous catheter.

BLOOD COLLECTION

A serial blood sampling was performed at the following time: T1 and T2 (with an hour apart) at two separate occasions; occasion 1 (distribution phase from day 1 or 2) and occasion 2 (steady phase from day 3 or 4). Each time the sampling was performed, a total of 3 ml of blood was withdrawn from a central line and transferred into heparinized tubes All samples were immediately kept in a

-4°C freezer and later were centrifuged at 3600 rpm for 10 minutes to separate plasma before stored in -80°C freezer prior to analysis. The antibiotic concentrations in plasma were measured using Liquid Chromatography Mass Spectrometry (LCMS) method with Ultraviolet (UV) detection.

CREATININE CLEARANCE MEASUREMENT

For measurement of creatinine clearance, 8-hours of urine output were collected on day-1. The creatinine clearance (CrCL) was calculated using the rate blanked, compensated, and uncompensated Jaffe technique, respectively. (Modular P and Cobas 6000, Roche Diagnostics GmbH, Mannheim, Germany).

$$\text{Creatine clearance (CrCL)} = \frac{\text{Urine Volume (ml) x urine creatinine (µmol/L) x 1.73}}{\text{Serum creatinine (µmol/L) x 480 x BSA}}$$

CrCL>>130 mL/min/1.73 m2 by an 8-hour urine creatinine collection is referred as Augmented Renal Clearance (ARC).

STATISTICAL ANALYSIS

A statistical analysis was performed using the statistical software package IBM-SPSS statistics version 20.0 (IBM Corp., New York, NY, USA). The sociodemographic data are expressed as mean ± SD, n (%), or median (lower quartile-upper quartile), and the association between ARC and sub-optimal PTZ concentration was analyzed by Chi-square test.

The variables or factors predicting sub-optimal PTZ concentrations and patient outcomes was assessed by multivariate logistic regression model with target attainment 100% for f T>MIC and target attainment 50% f T>MIC as dependent variable using the variables which gave a p value of <0.10 in the univariate analysis. The goodness of fit was assessed by the Hosmer-Lemeshow statistic. All tests were two-tailed, and P<0.05 was considered statistically significant.

RESULTS

A total of 43 patients were recruited in the study. Majority of them were female (60.5%) and Malay ethnicity (86%). The prevalence of ARC was 60.5% (Table I) and there was no significant difference in term of length of ICU/hospital stay and mortality (p>0.05).

Table I: Patients Demographics, Clinical Characteristics, and Outcomes

Variables	ARC (n= 26)	No ARC (n= 17)	p value
Age (years)	53.1 ± 18.4	57.53 ± 16.3	0.656
ETHNICITY			
Malay	22 (84.6)	15 (88.2)	0.310
Chinese	4 (15.4)	1 (5.9)	
Indian	0 (0.0)	1 (5.9)	
GENDER			
Male	12 (46.2)	5 (29.4)	0.272
Female	14 (53.8)	12 (70.6)	
Weight (kg)	63.8 ± 14.5	70.3 ± 19.4	0.739
Height (cm)	157.5 ± 8.0	157.9 ± 8.6	0.758
Baseline APACHE II Score	11.3 ± 2.5	10.9 ± 3.4	0.302
Baseline SOFA Score	3.4 ± 2.3	3.7 ± 2.3	0.852
Delta SOFA score D1-D4	0.85 ± 1.8	-1.1 ± 2.2	0.743
Charlson Index	3.7 ± 1.9	3.6 ± 1.7	0.521
Se Albumin (g/L)	27.5 ± 6.3	27.2 ± 7.8	0.393
Se Creatinine (µmol/L)	55.6 ± 15.3	68.2 ± 23.7	0.048
Cr Cl (ml/ min/1.73m^2)	296.6 ± 145.6	73.3 ± 34.7	<0.001
ADMISSION			
Medical	17 (65.4)	14 (82.4)	0.225
Surgical	9 (34.6)	3 (17.6)	
OUTCOME			
Length of ICU stay (days)	7.2 ± 4.4	9.4 ± 6.7	0.171
Length of Hospital stay (days)	28.3 ± 49.3	26.6 ± 35.8	0.900
ICU mortality	7 (26.9)	4 (23.5)	0.802
Hospital Mortality	8 (30.8)	5 (29.4)	0.925

Data expressed as mean ± SD, n (%), or median (lower quartile – upper quartile).

ARC: Augmented Renal Clearance with CrCL > 130ml/min/1.73m2

APACHE II Score: Acute Physiology and Chronic Health Evaluation II

SOFA score: Sequential Organ Failure Assessment Score

There was no significant difference in number of patients with ARC who achieved target MIC ≥16mg/1 PTZ at 50% interval between occasion 1 and 2 (p>0.05) (*Table II*). However, the number of patients with ARC reduced from occasion 1 (57.7%) to occasion 2 (42.3%) at 100% interval. For patients without ARC, the number of patients who achieved target MIC slightly reduced from occasion 1 to 2 at both 50% and 100% interval.

Table II: Association between patients with and without ARC and suboptimal therapeutic range at 4 different time point

Achieved target MIC (EUCAST ≥16 mg/L)	ARC N=26	No ARC N= 17	p value
Occasion 1 Time1 (50%fT>MIC)	22 (84.6)	17 (100)	
Time2 (100%fT>MIC)	15 (57.7)	17 (100)	0.091
Occasion2 Time3 (50%fT>MIC)	22 (84.6)	16 (94.1)	
Time4 (100%fT>MIC)	11 (42.3)	16 (94.1)	

Data expressed as mean ± SD, n (%) or median (lower quartile-upper quartile).

ARC: Augmented Renal Clearance with CrCL> 130ml/min/1.73m2

The concentration of PTZ was lower in ARC group compared to non-ARC group at 50% interval (Table III). Similar pattern was also observed at 100% interval where the PTZ concentration was significantly reduced from time 2 to time 4 (p<0.01) and PTZ concentration at time-4 was the lowest among all (23.2 ±23.1 mg/l).

Table III: Free Plasma concentration of Piperacillin-Tazobactam (PTZ) at 4 different time points in patients with ARC and without ARC.

Free Plasma Concentration of PTZ (mg/L)	ARC N=26	No ARC N= 17	p value
Occasion 1			
Time 1 (50%fT>MIC)	32.8 ±20.9	56.3 ± 26.2	<0.001
Time 2 (100%fT>MIC)	25.3 ±23.8	48.4 ± 17.2	
Occasion 2			
Time 3 (50%fT>MIC)	31.5 ±20.5	48.4 ± 17.2	
Time 4 (100%fT>MIC)	23.2 ±23.1	46.5 ± 29.6	

Data expressed as mean ± SD.

ARC: Augmented Renal Clearance with CrCL>130ml/min/1.73m

In addition, the ICU patients with ARC had a much higher rate of therapeutic failure than those without ARC, 57.7% and 5.9%, respectively (Table IV).

Table IV: Association between ARC and Therapeutic failure

	ARC N=26	No ARC N= 17	p value
Therapeutic Failure			
Yes	15 (57.7)	1 (5.9)	<0.001
No	11 (42.3)	16(94.1)	

Data expressed as median (%)

ARC: Augmented Renal Clearance with measured CrCL >130ml/ min/1.73m2

Therapeutic Failure: Free plasma concentration of PTZ > 16mg/L at any one of the time points

The multivariable regression analysis demonstrated a statistically significant association between patients' weight and their CrCL levels with suboptimal PTZ free plasma concentrations. This association was significant at the 0.05 and 0.002 levels. However, there was no significant differences were observed with respect to age, height, or baseline APACHE II score (Table V).

Table V: Multivariable Logistic Regression for suboptimal Piperacillin/ Tazobactam (PTZ) plasma concentration in ARC

Variables	Odds Ratio (95% CI)	p value
Age	1.00	0.80
Height (cm)	0.99	0.97
Weight (kg)	1.02	0.05
Baseline APACHE II Score	1.12	0.48
CrCl	1.01	0.002

Data expressed as Odds Ratio with 95% confidence interval

APACHE II Score: Acute Physiology and Chronic Health Evaluation II'

CrCL: Creatinine clearance

DISCUSSION

Our study represents a pioneering investigation in Malaysia, examining the interplay between augmented renal clearance (ARC) and the pharmacokinetics of β-lactam antibiotics such as Piperacillin-Tazobactam (PTZ) in critically ill patients. Through the development of a population pharmacokinetic model, we aimed to elucidate the impact of ARC on plasma concentrations of PTZ. A critically ill patients often experience altered pharmacokinetics due to the severity of their condition, leading to suboptimal medication levels. ARC, identified in 60% of our study cohort and reported in 20-65% of

critically ill patients elsewhere,[2,8] poses a significant challenge in achieving therapeutic drug concentrations particularly for renally eliminated antibiotics such as PTZ.[4]

Studies has extensively documented the implications of ARC on drug clearance, particularly related to antibiotics that primarily excreted by the kidneys.[12,14] Our findings corroborate existing literature demonstrating a high prevalence of ARC and its association with subtherapeutic antibiotic concentrations. Despite the administration of PTZ via continuous infusion, a significant proportion of patients with ARC had failed to reach the pharmacokinetic/pharmacodynamic (PK/PD) targets, raising concerns regarding treatment efficacy.

Continuous infusion of PTZ aimed at optimizing antibiotic exposure is a common practice in the ICU setting.[12,14] However, our study suggested that even this common practice may not guarantee the target attainment in patients with ARC. This highlights the critical need for personalized dosing strategies and vigilant monitoring of renal function to ensure adequate drug exposure and therapeutic efficacy.

Based on our study results, we believe that our study had made a significant contribution to the expanding body of literature on ARC and antibiotic pharmacokinetics in critically ill patients, particularly within the Malaysian context. By employing robust methodology, including liquid chromatography-mass spectrometry (LC-MS) with ultraviolet (UV) detection for plasma antibiotic measurements, we are offering a valuable insight into the pharmacokinetics of PTZ in patients with ARC.

Nevertheless, there were several limitations of our study that we should acknowledged. Firstly, the small sample size and single-centred design of our study may restrict the generalizability of our findings. Secondly, lack of the external validation for the population pharmacokinetic model and the absence of clinical outcome data underscores the need for further investigation. Thus, we would suggest that further studies should be conducted in the future aim to recruit a larger sample size and involve a multicentre cohorts encompassing diverse patient populations to validate our results and assess clinical outcomes comprehensively.

Our study findings underscore the necessity for more tailored antimicrobial therapy especially in critically ill patients with augmented renal clearance (ARC) and the initial dosing should be guided by CrCL to avoid falling below therapeutic thresholds. Additionally, determining pathogen minimum inhibitory concentrations (MICs) and applying therapeutic drug monitoring (TMD) can further optimize antibiotic exposure, considering the variability in local susceptibility patterns.

Although optimizing dosing regimens can be achieved through dosage adjustments or medication changes, clinicians should be vigilant regarding the adequacy of standard doses in patients exhibiting ARC. Further research looking into innovative administration strategies for this patient population should be prompted. Thus, exploring alternative dosing strategies that may have a potential to improve the outcomes and reduce risks of treatment failure is imperative.

Moving forward, clinical practice guidelines may need to incorporate considerations for ARC, emphasizing personalized dosing approaches based on individual patient characteristics. Furthermore, ongoing research should focus more on developing and validating novel dosing algorithms specifically tailored for critically ill patients with ARC, ultimately enhancing therapeutic efficacy and minimizing the emergence of antimicrobial resistance.

In summary, addressing the impact of ARC on antibiotic dosing represents a critical step towards optimizing treatment outcomes in critically ill patients. By adopting individualized dosing strategies and leveraging innovative approaches, clinicians can navigate better the complexities of antimicrobial therapy in this vulnerable patient population, ultimately improving patient care and reducing the burden of infectious diseases in intensive care settings.

CONCLUSION

In conclusion, while continuous administration of PTZ 16g/2g/day is believed to be the best practice for critically ill patients, those with a high creatinine clearance (CrCL) above 130 mL/min remain at risk of receiving suboptimal doses. These patients may require higher doses of Piperacillin/Tazobactam than currently licensed, without increasing the risk of overdose or neurotoxicity.

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