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Pharmacokinetics of Piperacillin in Critically Ill Australian Indigenous Patients with Severe Sepsis

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There are no available pharmacokinetic data to guide piperacillin dosing in critically ill Australian Indigenous patients despite numerous reported physiological differences. This study aimed to describe the population pharmacokinetics of piperacillin in critically ill Australian Indigenous patients with severe sepsis. A population pharmacokinetic study of Indigenous patients with severe sepsis was conducted in a remote hospital intensive care unit. Plasma samples were collected over two dosing intervals and assayed by validated chromatography. Population pharmacokinetic modeling was conducted using Pmetrics. Nine patients were recruited, and a two-compartment model adequately described the data. The piperacillin clearance (CL), volume of distribution of the central compartment (V_c), and distribution rate constants from the central to the peripheral compartment and from the peripheral to the central compartment were 5.6 ± 3.2 liters/h, 14.5 ± 6.6 liters, 1.5 ± 0.4 h^{-1}, and 1.8 ± 0.9 h^{-1}, respectively, where CL and V_c were found to be described by creatinine clearance (CL_{CR}) and total body weight, respectively. In this patient population, piperacillin demonstrated high interindividual pharmacokinetic variability. CL_{CR} was found to be the most important determinant of piperacillin pharmacokinetics.

Critically ill Australian Indigenous patients have a high mortality rate (1–3). They are reported to be younger and have greater disease severity and more comorbidity upon admission into the intensive care unit (ICU), of which sepsis and severe sepsis are common admission diagnoses (1–3). Unfortunately, the lack of evidence-based antibiotic dosing guidelines in the Indigenous population makes prescribing a significant challenge for clinicians.

The Australian Indigenous are reported to have various physiological differences compared with non-Indigenous Australians. For instance, young and healthy Indigenous adults have approximately 30% fewer nephrons than their non-Indigenous counterparts (4). From an anthropometric perspective, they generally have slightly lower total body weight (TBW), higher central fat, and slimmer extremities (5). While strong comparative data on interethnic antibiotic pharmacokinetics generally remain elusive, a recent systematic review has suggested the possibility of interethnic differences in antibiotic pharmacokinetics for numerous antibiotics (6).

Piperacillin is a broad-spectrum antibiotic commonly used in the critically ill and is considered to have time-dependent bacterial kill characteristics. Its hydrophilic physicochemistry makes it prone to pharmacokinetic fluctuations in critically ill patients (7). To date, there are no data on piperacillin pharmacokinetics in critically ill Indigenous Australians.

The aim of this study was to describe the population pharmacokinetics of piperacillin in critically ill Australian Indigenous with severe sepsis.

MATERIALS AND METHODS

Setting. An observational population pharmacokinetics study was conducted in a 10-bed ICU at a teaching hospital in remote Central Australia. Ethics clearance was obtained from the local and university ethics committees (Central Australian Human Research Ethics Committee, approval HREC-13-149; The University of Queensland Human Research Ethics Committee, approval 2013000904).

Study protocol. The dosing regimen for piperacillin, which was coadministered with tazobactam (Tazopip; Aspen Pharmacare, Sydney, Australia), was at the discretion of the treating intensivist. Inclusion and exclusion criteria, details of sampling, demographic data collected, and sample handling were previously published (8).

Drug assay. Piperacillin was measured in plasma (0.5 to 500 mg/liter) by a validated ultra-high-pressure liquid chromatography–tandem mass spectrometry spectroscopy (UHPLC-MS/MS) method on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan). The methods for this assay have been described previously (9). The assay method was validated for linearity, matrix test, selectivity, lower limit of quantification, recovery, reinjection stability, precision, and accuracy using the Food and Drug Administration criteria for bioanalysis (10). Precision was within 5.8% and accuracy was within 10.0% at the tested plasma quality control piperacillin concentrations of 1.5, 50, and 400 mg/liter.

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TABLE 1 Demographic and clinical data

Parameter[a]	Value ($n = 9$)[b]
Age (yr)	43 ± 11
Female (no.)	4 (44)
Wt (kg)	76 ± 11
Height (cm)	170 ± 17
BMI (kg/m^2)	27 ± 7
Serum creatinine concn (μmol/liter)	95 ± 69
CL_{CR} (ml/min)	91 ± 46
Serum albumin concn (g/liter)	27 ± 5
Vasopressor use (no.)	8 (89)
APACHE II score	23 ± 6
SOFA score	8 ± 2

[a] BMI, body mass index; CL_{CR}, measured creatinine clearance; APACHE II score, acute physiological and chronic health evaluation II score; SOFA score, sequential organ failure assessment score.
[b] Data are presented as mean ± standard deviation or as number (percent).

Population pharmacokinetic modeling. Concentration-time data obtained from the plasma samples were described by compartment models using the Pmetrics software package (11) for R (version 3.2.2). Demographic and clinical data collected were tested for inclusion into the pharmacokinetic model as covariates. The covariates which statistically improved the log likelihood ($P < 0.05$) and/or improved the goodness-of-fit plots were retained in the final model.

Model diagnostics. Model evaluation was performed by visually assessing the goodness of fit of the observed-predicted plots and the coefficient of determination of the linear regression of the observed-predicted values (r^2 close to 1, intercept close to 0) from each run. The predictive performance was assessed on mean prediction error (bias) and the mean biased adjusted squared prediction error (imprecision) of the population and individual posterior predictions. Visual predictive check plots (VPC) generated from the final model were also visually assessed to determine whether the observed data were appropriately distributed within the simulated model.

Statistical analysis. Continuous data were presented as mean ± standard deviation or median ± interquartile range and categorical data presented as counts (percent).

RESULTS

Ten Indigenous patients were recruited, and one patient was excluded due to inappropriate storage of samples. The demographics and clinical information are presented in Table 1. In total, 139 plasma samples were available for pharmacokinetic analysis.

Population pharmacokinetic model building and model diagnostics. A two-compartment model was found to describe the data adequately. Elimination from the central compartment (represented by clearance [CL]) and intercompartmental distribution

TABLE 2 Pharmacokinetic parameter estimates from two-compartment model[a]

Parameter	Total ($n = 9$)[b]	CV (%)	Variance	Median
V_c (liters)	14.5 ± 6.6	45.7	44.0	12.2
CL (liters/h)	5.6 ± 3.2	57.0	10.4	4.6
K_{cp} (h^{-1})	1.5 ± 0.4	28.2	0.2	1.5
K_{pc} (h^{-1})	1.8 ± 0.9	47.5	0.7	1.7

[a] V_c, volume of distribution in the central compartment; CL, drug clearance; K_{cp}, distribution rate constant from central to peripheral compartment; K_{pc}, distribution rate constant from peripheral to central compartment; CV, coefficient of variation.
[b] Data are presented as mean ± standard deviation.

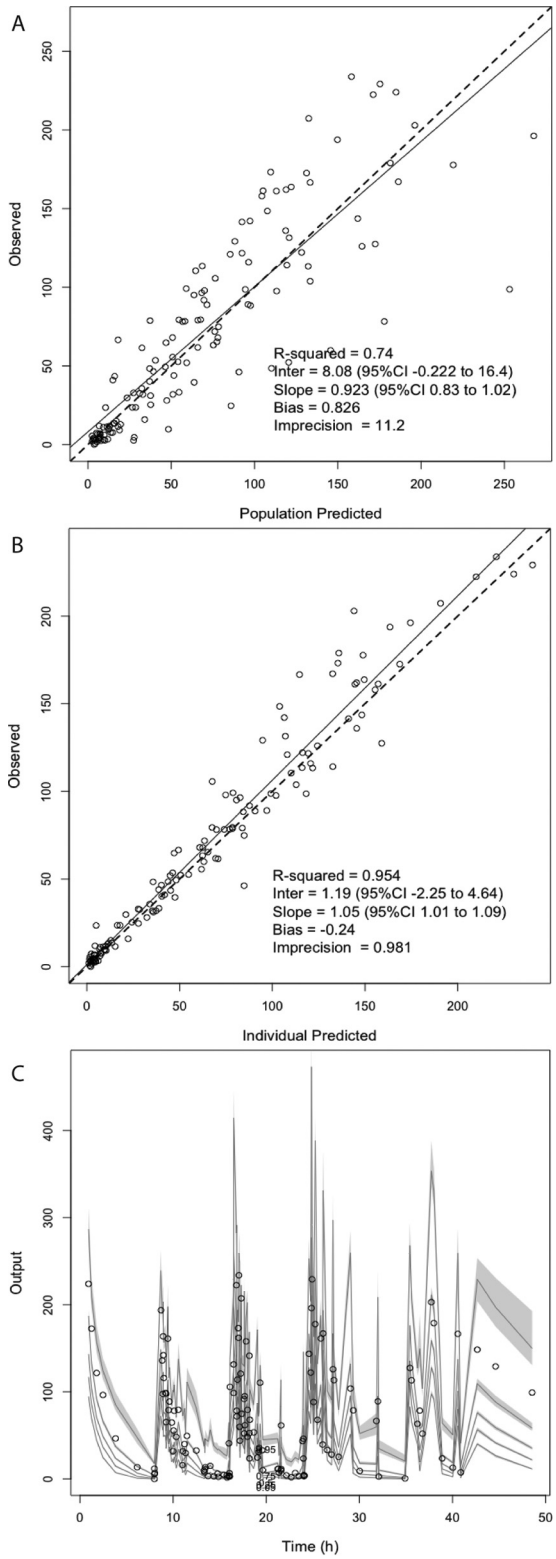

FIG 1 Diagnostics of final pharmacokinetic model. (A) Plot of population predicted concentrations versus observed concentrations. (B) Plot of individual predicted concentrations versus observed concentrations (where the data presented on both the *x* and *y* axes are concentrations in milligrams per liter). (C) Visual predictive check plot (where output on the *y* axis is concentration in milligrams per liter).

TABLE 3 Pharmacokinetic parameter estimates of piperacillin from published studies[a]

Dose regimen (reference)	Population	No. of females/ total	Age (yr)	Wt (kg)	CL_{CR} (ml/min)	SOFA score	APACHE II score	Pharmacokinetic parameters	
								V_c (liters/kg)	CL (liters/h)[b]
4-g 30-min infusion (present study)	Severe sepsis, Australian Indigenous	4/9	43 ± 11	76 ± 11	91 ± 46	7.8 ± 1.7	23 ± 6	0.19 ± 0.09	5.6 ± 3.2
60-mg/kg 3-min bolus (12)	Healthy volunteers	0/12	20–30	69	NA	NA	NA	NA	*11.3 ± 1.3*
4-g 3-min bolus (13)	Healthy volunteers	0/5	22 ± 0.4	70 ± 1.4	87 ± 5	NA	NA	0.16 ± 0.03	*15.3 ± 1.2*
4-g 30-min infusion (14)	Abdominal infection	1/18	31 ± 9	76 ± 17	98 ± 26	NA	NA	NA	14.8 ± 4.0
4-g 30-min infusion (15)	Elective colorectal surgery	9/18	67 ± 12	72 ± 11	72 ± 21	NA	NA	NA	11.6 ± 2.6
4-g, administration duration not specified (16)	Community-acquired pneumonia	14/53	65 ± 17	56 ± 12	81 ± 47	NA	NA	NA	8.2 ± 2.6
4-g bolus (17)	Hospitalized patients	2/12	60 ± 12	70 ± 13	60 ± 31	NA	NA	NA	5.7
4-g 20-min infusion (18)	Sepsis, critically ill	3/8	38 (22–65)	80 (74–86)	88 (53–101)	3 (3–3)	24 (18–26)	0.09 [0.07–0.12]	17.1 [14.4–20.6]
4-g 20-min infusion (19)	Ventilator-associated pneumonia, critically ill	3/7	42 (23–65)	85 (72–90)	166 (103–237)	3 (2–3)	24 (16–27)	0.17 [0.14–0.19]	NA
30-min infusion, dose not specified (20)	Sepsis/severe sepsis	?/14	NA	NA	52 (21–123)	9 (5–14)	NA	NA	6.2 (1.1–30.7)
4-g 20-min infusion (21)	Sepsis, critically ill	21/48	47 ± 18	88 ± 24	122 ± 59	3.5 (2–6)	19 ± 7	0.23	16.3
30-min infusion, dose not specified (22)	Critically ill	26/38	62 (54–68)	70 (60–81)	47 (29–87)	11 (8–13)	20 ± 6.0	NA	2.3 (1.7–3.7)
4-g 30-min infusion (23)	Critically ill	?/19	NA	NA	NA	NA	NA	NA	3.2 {0.8–32.8}
30-min infusion, dose varied (24)	Surgical, critically ill	5/13	45 ± 19	79 ± 18	139 ± 44	6 ± 2	15 ± 5	NA	40.4

[a] Abbreviations: CL_{CR}, creatinine clearance; SOFA score, sequential organ failure assessment score; APACHE II score, acute physiologic assessment and chronic health evaluation II score; V_c, volume of distribution of the central compartment; CL, drug clearance; NA, data not available. Data are presented as mean ± standard deviation, median (interquartile range), median [95% confidence interval], or median {range}.

[b] Data in italic were not directly reported but were calculated from pharmacokinetic data in the study.

(represented by distribution rate constants from the central to the peripheral compartment [K_{cp}] and from the peripheral to the central compartment [K_{pc}]) were modeled as first-order processes using differential equations. Creatinine clearance (CL_{CR}) and the patient's TBW were the only covariates tested which significantly improved the pharmacokinetic model. The final model was described by the equations $TVCL = CL \times [(CL_{CR}/55) + 0.45]$ and $TVV_c = V_c \times (TBW/76)^{0.75}$, where TVCL is the typical value of piperacillin clearance, CL is the population parameter estimate of piperacillin clearance, TVV_c is the typical value of volume of distribution of the central compartment, V_c is the population parameter estimate of volume of the central compartment, and TBW is total body weight. The final covariate model had a decrease in −2 log likelihood of 33.6 from the base model and improved the goodness-of-fit plots. The population pharmacokinetic parameter estimates obtained in the two-compartment model are presented in Table 2.

The goodness of fit for the plots of individual and population predicted versus observed values and the VPC were considered acceptable (Fig. 1). The VPC showed an even distribution of the observed data across the percentiles of the simulated data.

Table 3 compares the pharmacokinetic parameter estimates observed in our study with other published data from various patient populations (12–24). The parameter estimates from the present study generally show a lower mean piperacillin CL than data on healthy volunteers and critically patients when CL_{CR} was taken into consideration. On the other hand, V_c values were similar across all patient groups.

DISCUSSION

To the best of our knowledge, this is the first study to examine the population pharmacokinetics of piperacillin in critically ill Australian Indigenous patients with severe sepsis. We found that piperacillin pharmacokinetics in this population have high interindividual variability compared to those in healthy volunteers (12, 13) but are similar to those in other critically ill or hospitalized patients (14–24). Nonetheless, we have also found that renal function, i.e., CL_{CR}, remains the most important determinant of piperacillin dosing requirements.

The mean CL estimate observed in this study was 5.6 liters/h, which is lower than previously described for healthy volunteers (12 to 14 liters/h). However, individual estimates in our study group ranged from 2.8 to 14.2 liters/h, which is not dissimilar to the range of other published data for critically ill or hospitalized patients (3 to 40 liters/h) (14–24). Regarding piperacillin volume of distribution, the V_c in this study was similar to other published data for both healthy volunteers and critically ill patients (13, 18, 19, 21). These data highlight why there is such high variability in piperacillin pharmacokinetics, where both supra- and subtherapeutic concentrations were common.

It is likely that the high interindividual pharmacokinetic differences observed in this study prevented identification of any interethnic differences, if such an effect is indeed present. This conclusion is supported by a recent systematic review that suggests that antibiotics which are eliminated predominantly via glomerular filtration are less likely to display interethnic pharmacokinetic differences (6), in part because the differences can be readily explained by renal function estimates. Whether the lower mean piperacillin CL observed in our study group, when CL_{CR} was taken in consideration, is caused by a lower nonrenal clearance requires further investigation (14–16, 18, 20).

This study has some limitations. First, only plasma piperacillin concentrations were assessed in this study, which do not reflect piperacillin concentrations achieved in other tissue sites (25). Second, the study was not designed to investigate the unbound piperacillin concentration, and an assumption of 30% albumin binding was made for our dosing simulations. This is supported by previous literature (26). Lastly, patients recruited in this study met the severe sepsis criteria defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee (27), and the study recruitment took place prior to the publication of the new definition for "sepsis" (28). We acknowledge that the two definitions may result in slightly different patient groups, and there are few data currently available to define how different the groups may be.

In conclusion, this study has highlighted that CL_{CR} is the strongest determinant of piperacillin pharmacokinetics in severely septic Australian Indigenous patients. Therefore, it should be considered essential to select the dosing regimens for individual patients according to their measured CL_{CR}.

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