JPPT | Case Report

Piperacillin Pharmacokinetics in a Pediatric Patient With Primary Hyperoxaluria Receiving High-Dose Continuous Dialysis Post Liver-Kidney Transplant

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Continuous kidney replacement therapy (CKRT) can influence pharmacokinetics (PK), including clearance (CL) of antibiotics like piperacillin (PIP). Both CKRT intensity, or "dialysis dose," and residual kidney function can alter PIP PK and pharmacodynamic (PD) target attainment (TA), defined by the percentage of time free PIP concentrations exceed the minimum inhibitory concentration (% *f*T > MIC). In existing reports, children receiving PIP and CKRT are usually oligoanuric, so PIP PK/PD in non-oligoanuric patients receiving high-intensity CKRT is unknown. This report analyzes free PIP PK/PD in a child with robust kidney function who received 30-minute infusions of 100 mg/kg PIP-tazobactam every 6 hours while on high-intensity CKRT after liver-kidney transplant for primary hyperoxaluria. Model-informed PK software was used to estimate PK/PD parameters for periods on and off CKRT. PIP CL on CKRT was 66% higher than off CKRT (5.59 L/hr vs 3.36 L/hr). Nearly 100% *f*T > 1xMIC (using 8 mg/L for Enterobacterales) was achieved whether on or off CKRT, but only 60% *f*T > 4xMIC was achieved on CKRT. CKRT CL was 40% of total CL on CKRT and 51% of the CKRT dialysis dose, suggesting PIP elimination was mostly renal despite high-intensity dialysis. Monitoring of free PIP concentrations may help ensure proper TA in non-oligoanuric patients receiving high-dose CKRT.

ABBREVIATIONS AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; CL, clearance; CL_{EC}, extracorporeal clearance; *f*T >, time free concentration exceeds; f_u, fraction unbound; MIC, minimum inhibitory concentration; MW, molecular weight; PD, pharmacodynamic; PH1, primary hyperoxaluria type 1; PIP, piperacillin; PK, pharmacokinetic; PTZ, piperacillin-tazobactam; Q, intercompartmental clearance; Q_{ef}, total effluent flow; Q_{uf}, ultrafiltration rate; TA, target attainment; TM_{50}, maturation half-life; UOP, urine output; V_d, volume of distribution; V_1, central volume of distribution; V_2, peripheral volume of distribution; % fT > MIC, percentage of time free PIP concentrations exceed the minimum inhibitory concentration

KEYWORDS continuous kidney replacement therapy; dialysis; pharmacodynamics; pharmacokinetics; piperacillin; primary hyperoxaluria

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Information Box

- What specific questions does this report address?
  - Appropriate piperacillin dosing for a pediatric patient receiving high-dose continuous kidney replacement therapy (CKRT) alongside significant intrinsic kidney function is unknown.
- What does this report add to our current knowledge?
  - While the patient was on high-dose CKRT, clearance of piperacillin was higher than while the patient was off CKRT, and residual kidney function contributed to a substantial proportion of clearance; therefore, stringent pharmacodynamic target attainment was inadequate when on high-dose CKRT.

Introduction

Continuous kidney replacement therapy, or CKRT, is a type of continuous dialysis typically used to support patients with severe acute kidney injury (AKI), intoxications, or fluid overload.[1] Patients who receive CKRT are often oligoanuric, but CKRT can be used in non-oligoanuric patients for supplemental toxin removal.[1] Extracorporeal clearance (CL_{EC}), or solute removal via CKRT, is possible when the solute is smaller than the pore size of the CKRT filter (molecular weight [MW] <35 kDa using modern CKRT filters[2]), has a low volume of distribution (V_d), and is not highly bound to plasma proteins. The solutes removed include toxins that accumulate with kidney dysfunction and some medications, including many antibiotics. Antibiotics are commonly administered to children receiving CKRT, as sepsis is a leading cause of AKI requiring CKRT,[3] and

the presence of an indwelling hemodialysis catheter predisposes to infection. However, there is a paucity of data regarding antibiotic pharmacokinetics (PK) and pharmacodynamics (PD) in children receiving CKRT, especially in patients who are non-oligoanuric.[4]

Piperacillin-tazobactam (PTZ) is a beta-lactam/beta lactamase inhibitor combination commonly used in critically ill children given its broad-spectrum activity, which includes anaerobic and antipseudomonal coverage.[5] Piperacillin (PIP), the active antimicrobial component, has a MW of 518 Da and is approximately 30% protein bound,[6] rendering it susceptible to CL_{EC} via CKRT. Optimal bactericidal activity of PIP depends on the percentage of time that free PIP concentrations are above the minimum inhibitory concentration, or MIC (% *f*T > MIC). A lack of consensus about precise PD targets exists due to limited data associated with clinical outcomes, but typically, more stringent PD targets are recommended for critically ill patients.[7] Expert reviews have suggested that targets such as 100% *f*T > 1xMIC and 100% *f*T > 4xMIC could be necessary for maximum efficacy of PIP and minimum emergence of resistance.[7,8]

Previous studies in adults have quantified the effects of CKRT on PIP PK. A review reported a median additional CL_{EC} of 1.43 L/hr, which contributed to a 66% increase in total clearance (CL) while on CKRT (median body CL = 2.76 L/hr). This review suggested that the use of continuous infusions could help attain stringent PD targets in the setting of this additional $CL_{EC.}$[9]

Pediatric data on PIP PK/PD in patients supported with CKRT are comparatively limited, with only 3 published reports to our knowledge. In a PIP PK and dose optimization study of 32 critically ill children receiving CKRT, Thy et al[10] created a population PK model to simulate different dosing regimens. Because only 53% of the patients were anuric, and 25% had urine output (UOP) >0.3 mL/kg/hr, they could only assess the effect of residual renal function on PIP PD target attainment (TA) to an oliguric threshold of 0.5 mL/kg/hr. Through simulating different levels of UOP up to 0.5 mL/kg/hr, they recommended using higher doses with continuous infusions for patients with modest residual renal function. A second population PIP PK study in critically ill children by Butragueño-Laiseca et al[11] included 13 (41% of total included) patients on CKRT. Only 3 of those patients had any residual UOP. Using the model that they created, they recommended PIP drug monitoring and either intermittent or continuous infusion dosing regimens for patients on CKRT. Finally, a case study on PIP PK in a child with liver failure who received concomitant molecular adsorbent recirculating system therapy and CKRT reported on PIP PK for 1 cycle of CKRT alone.[12] The authors found an increase in CL from baseline to during CKRT alone (2.0 L/hr vs 3.0 L/hr, 50% increase) and adequate TA on CKRT alone. Residual UOP was not reported. This last case report is the only one of the 3 articles that reported using free PIP concentrations. Measuring free concentrations directly obviates the need to rely on an assumption of a fixed percentage of protein binding, which is known to fluctuate in the context of critical illness.[13] Thus, there is a knowledge gap regarding free PIP PK in critically ill children receiving CKRT with significant residual kidney function.

Because blood flow rates are typically much faster than dialysis fluid flow rates in CKRT, the total effluent flow (Q_{ef}) is the main driver of solute removal in CKRT[1] and can affect antibiotic CL_{EC}. Q_{ef} can be considered the overall dialysis dose, and the standard pediatric dialysis dose is around 2000 mL/hr/1.73 m^2.[14] High-dose or high-intensity dialysis involves an effluent flow rate significantly above that standard. The aforementioned studies also do not elucidate the potential effect of high Q_{ef} on PIP CL or TA. Therefore, there also remains a knowledge gap in PIP PK regarding the effects of high-dose dialysis in the setting of preserved intrinsic kidney function.

This case study describes the unique PK/PD of free PIP in a child receiving high- dose CKRT for oxalate CL after combined liver-kidney transplant for primary hyperoxaluria who had intrinsic kidney function from the new allograft. We report CL, V_d, and TA, by estimating the percent time free PIP concentrations remain above 1x MIC (*f*T > 1xMIC) and 4x MIC (*f*T > 4xMIC).

Case Report

Patient Background. The 8-year-old, 23.5-kg (0.86 m^2) boy described here was enrolled in a larger PK/PD study of beta-lactam antibiotics in critically ill children that received institutional review board approval at our institution. The patient had received 1 prior kidney transplant owing to presumed renal dysplasia. He was thereafter diagnosed with primary hyperoxaluria type 1 (PH1) when his initial posttransplant course was complicated by severe persistent AKI.[15] PH1 is a rare genetic disorder that causes a deficiency of alanine-glyoxylate aminotransferase, a peroxisomal liver enzyme. This deficiency leads to the inability to properly metabolize glyoxylate, which is subsequently transformed into oxalate. The consequent oxalate excess results in toxicity to the kidneys, retina, bone, heart, and other organs.[16] His first allograft was salvaged with high-intensity CKRT and intermittent hemodialysis to remove excess oxalate along with lumasiran, a small interfering RNA that decreases hepatic oxalate production.[15–17] Despite these interventions, he developed posttransplant chronic kidney disease stage IV and subsequently received a combined liver-kidney transplant.

To minimize nephrotoxic effects from oxalate buildup in the new kidney allografts, the patient received high-dose CKRT (delivered Q_{ef} ~9000 mL/hr/1.73 m^2) during and immediately after transplant to augment renal oxalate CL. He had immediate good function of both the liver and paired kidney allografts, based on normal

hepatic synthetic function and robust urine output. He was prescribed PTZ as peri-transplant infection prophylaxis in alignment with the institution's standard liver transplant protocol.

Given the unique combination of high-dose CKRT alongside significant intrinsic renal function from the newly transplanted kidneys, we sought to characterize PIP PK in this patient.

Study Period PIP and CKRT Data. The patient was supported with continuous veno-venous hemodialysis, a modality of CKRT that can efficiently remove small molecules such as oxalate.[18,19] The filter used was the HF1000 (1.1 m^2; Baxter, Deerfield, IL), and the prescribed blood flow, dialysate flow, and replacement fluid flow rates were 150 mL/min, 4000 mL/hr, and 50 mL/hr, respectively. The patient had robust UOP, which averaged 2.26 mL/kg/hr during the study period. To ensure adequate perfusion of the new renal allograft, the CKRT was prescribed to remove only the volume of the calcium and citrate infusions provided for regional anticoagulation. This practice contrasts with the fluid removal strategy for patients with fluid overload or oligoanuria in which all fluids administered to the patient are typically removed during CKRT. The net volume removed is known as the net ultrafiltration rate (net Q_{uf}), which is calculated by subtracting the volume put into the circuit (priming volume) from the ultrafiltrate volume removed. The total dialysis dose, Q_{ef}, is the sum of dialysate flow rate, replacement fluid flow rate, and net Q_{uf}. The patient's average delivered Q_{ef} was 4406 mL/hr, approximately 4.5 times the typical pediatric dialysis dose when indexed to body surface area (8863 mL/hr/1.73 m^2 vs 2000 mL/hr/1.73 m^2).

At our institution, weight-based dosing is calculated for the PTZ combination, of which PIP comprises 89% of the total. Postoperatively, the patient was administered 100 mg/kg PTZ every 6 hours as a 30-minute infusion throughout the time he was on CKRT.

Methods

PK/PD Analysis. We analyzed free PIP concentrations immediately postoperatively and through the end of PTZ treatment, a period that spanned 7 days. Free PIP concentrations were measured from residual blood samples obtained from clinical samples through a random scavenged opportunistic sampling strategy.[20] Samples were stored at 4°C and centrifuged within 7 days for plasma extraction. Plasma was stored at −80°C until free drug was isolated with ultrafiltration, and free concentrations were measured by using a high-performance liquid chromatography assay previously validated by our group.[20]

PIP doses and free concentrations were entered into a precision dosing software, MwPharm++ (Mediware, Prague, Czech Republic), to estimate concentration vs time profiles as well as CL and central volume of distribution (V_1). To conduct the PK modeling for this patient, a previously published population PK model describing PIP in critically ill children,[21] adapted for free PIP by assuming 30% protein binding, was used because there is no available published model with free PIP concentrations at this time. Weight and post-menstrual age (PMA) are included as covariates in this model, and allometric scaling was used to scale the median body weight of 14 kg to 70 kg for use in MwPharm++. PMA was included as a maturation sigmoidal function $\left(F_{mat} = \frac{PMA^{HILL}}{TM_{50}^{HILL} + PMA^{HILL}}\right)$, though this was not influential on this patient's CL because he was significantly older than the maturation half-life (TM_{50}) of 61 weeks.[21] Intercompartmental CL (Q) and peripheral compartment V_d (V_2) were fixed to the population mean established by the model and adapted to free concentrations (Q = 13 L/hr/70 $kg^{0.75}$ and V_2 = 11.37 L/70 kg).

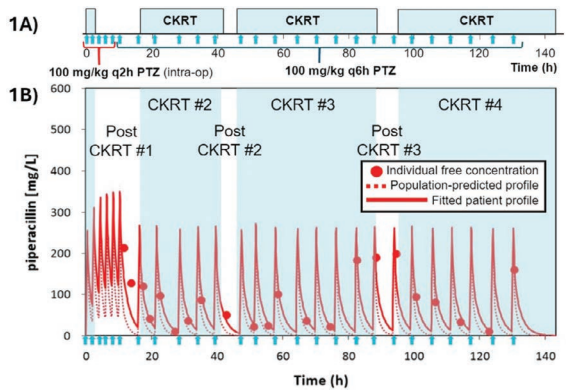
Analysis of the observed free concentrations was completed by using Bayesian estimation with an assay error of 5%, aligning with the test-retest variability of our clinical laboratory. Concentration vs time profiles were generated and used to find the CL and V_1 for each period on and off CKRT (Figure A). Serial fits were obtained by inputting all PIP doses prior to the period of interest, then fitting the concentration-time profile using only the concentrations available during the period of interest. Time-weighted arithmetic means of PK parameters were then calculated as based on the time the patient spent in each period to determine average PK parameters for time on- and off-circuit. These fits were also used to assess PD TA as % *f*T > 1xMIC and % *f*T > 4xMIC. The empiric selected MIC was 8 mg/L—the Clinical Laboratory and Standards Institute PIP breakpoint for Enterobacterales—because no bacteria were cultured from the patient.[22]

Clinical Data and Outcomes. Chart review of electronic medical record was conducted to obtain information about clinical history, demographics, potential infections, urine output, and kidney-/liver-related laboratory values. The initiation and cessation of CKRT periods were recorded in addition to blood flow, dialysate flow, and replacement fluid rates. Because creatinine is easily cleared by CKRT, creatinine was not a valid kidney function biomarker post-transplant, so serum creatinine data were not reported.

Results

Twenty-two free PIP concentrations were analyzed from scavenged plasma samples, 17 of which were obtained when the patient was receiving CKRT. The concentration-vs-time profile for the entire study period is displayed in Figure B. Each period on and off CKRT was analyzed individually, and the PK results are summarized in Table 1. Average urine outputs and albumin levels on each study day are reported in Table 2. The weighted mean PIP CL for all cycles when the patient was

Figure. Piperacillin concentration-time profile for periods on and off CKRT.



CKRT, continuous kidney replacement therapy; CL, clearance; PIP, piperacillin; PTZ, piperacillin-tazobactam; V_d, volume of distribution.

(A) The PTZ dosing regimen received by the patient relative to time 0, which represents the first dose of PTZ given. Times when the patient was on CKRT are indicated by light blue boxes. Each dose is represented by a blue arrow underneath the x-axis. (B) Concentration (PIP in mg/L) vs time (in hours) profile for the entire study period, with periods on and off CKRT labeled accordingly. Periods on CKRT are highlighted in light blue. The red circles are observed free concentrations. The dashed line is the population-predicted profile based on doses and covariates, while the solid line is the fitted individual-predicted line accounting for both the model and the concentrations with Bayesian estimation. For this figure, all the observed concentrations were fitted at once, but when estimating CL and Vd, the concentrations were fit phase by phase (e.g., post CKRT #1, CKRT #2).

on CKRT was 5.59 L/hr (13.1 L/hr/70 kg$^{0.75}$). The weighted mean PIP CL for all cycles off CKRT was 3.36 L/hr (7.88 L/hr/70 kg$^{0.75}$). Thus, mean CL_{EC} was 2.23 L/hr, increasing total CL by 66% while on CKRT vs while off CKRT (Table 3). This CL_{EC} was 40% of total patient CL while on CKRT and 51% of the total dialysis dose of ~4.4 L/hr.

The weighted mean PIP V_1 was larger while the patient was on CKRT vs off CKRT (18.25 L/70 kg vs 15.89 L/70 kg). Of note, the PIP V_1 for the first period off CKRT, immediately postoperatively, was elevated (18.20 L/70 kg) as compared with the estimated V_1 during other periods off CKRT (14.28 and 13.18 L/70 kg). The patient's net intake for the first period off CKRT was +4760.6 mL (366.2 mL/hr). PD results are summarized in Table 1. *f*T > 1xMIC approached or achieved 100% for all periods analyzed. *f*T > 4xMIC while the patient was on CKRT was 60% as compared with 97% when off CKRT.

Discussion

This case report of a child receiving high-dose CKRT after combined liver-kidney transplant demonstrates that CKRT was associated with higher PIP CL and decreased PD TA. For a target of 100% *f*T > 1xMIC, the target was achieved while off CKRT and nearly achieved while on CKRT. However, % *f*T > 4xMIC was much lower than 100% (60.3%) while on CKRT. Because the patient had immediate kidney allograft function post transplant, he had antibiotic elimination from both intrinsic kidney function and

Table 1. PK and Target Attainment Results From Each Period On and Off CKRT*

	Periods Off CKRT			Periods On CKRT		
Time of each period, hr	13.1	4.75	8.37	24.5	42.8	45.3
Total CL, L/hr (L/hr/70 kg$^{0.75}$)	3.35 (7.84)	3.91 (9.17)	3.08 (7.21)	5.19 (12.14)	5.65 (13.22)	5.76 (13.49)
	Weighted Mean: 3.36 (7.88)			**Weighted Mean: 5.59 (13.1)**		
V_1, L (L/70 kg)	6.11 (18.20)	4.80 (14.28)	4.42 (13.18)	5.57 (16.58)	6.71 (19.99)	5.88 (17.52)
	Weighted Mean: 5.33 (15.89)			**Weighted Mean: 6.13 (18.25)**		
% *f*T > 1xMIC	100	100	100	98.97	97.70	98.40
	Weighted Mean: 100			**Weighted Mean: 98.3**		
% *f*T > 4xMIC	100	91.62	100	67.70	60.60	55.98
	Weighted Mean: 98.5			**Weighted Mean: 60.3**		

CKRT, continuous kidney replacement therapy; CL, clearance; MIC, minimum inhibitory concentration; PIP, piperacillin; PK, pharmacokinetic; Q, intercompartmental clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution; % fT > 1xMIC, percentage of time free PIP concentrations exceed 1x the minimum inhibitory concentration; % fT > 4xMIC, percentage of time free PIP concentrations exceed 4x the minimum inhibitory concentration

* CL, V_1, and fT > 1x-4xMIC for periods on and off CKRT. CL was allometrically scaled to body weight as dictated by the population PIP PK model for critically ill children.[21] V_2 (11.37 L/70 kg) and Q (13 L/hr/70 kg$^{0.75}$) were fixed according to the model population mean. Means are weighted as based on time of each period.

Table 2. Urine Output and Albumin Concentrations*

Study Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Mean
Urine output, mL/kg/hr	1.94	2.71	1.72	3.54	2.91	2.24	0.76	2.26
Albumin, g/dL	2.2	3.3	3.8	3.5	2.8	2.7	2.5	3.0

PTZ, piperacillin-tazobactam

* Average urine output (mL/kg/hr) and albumin levels (g/dL) for each day PTZ was administered. Note that the urine output far exceeded the threshold for oliguria (<0.5 mL/kg/hr).

Table 3. Comparisons of CL Provided by CKRT*

Weighted Mean CL While on CKRT, L/hr	Weighted Mean CL While off CKRT, L/hr	CL_{EC}, L/hr	Increase in Total CL With CKRT	CL_{EC}/Total CL While on CKRT	CL_{EC}/ CKRT Dose
5.59	3.36	2.23	66%	40%	51%

CKRT, continuous kidney replacement therapy; CL, clearance; CL_{EC}, extracorporeal clearance; PIP, piperacillin

* CKRT-provided PIP CL, or CL_{EC}, as calculated from the difference of PIP CL on vs off CKRT and compared with total CL while on CKRT and the total CKRT dose (about 4.5 L/hr).

from CKRT in the form of CL_{EC}. This additional CL_{EC} explains the lower PD TA for on-circuit periods. However, CL_{EC} was only 40% of total patient CL while on CKRT, suggesting that the majority of PIP elimination was from the patient's newly transplanted kidneys despite high-dose dialysis.

Because the dialysis dose (Q_{ef}) is the primary driver of solute removal in CKRT, and this patient was receiving a dose approximately 4½ times that of standard pediatric CKRT, it is interesting to note that PIP CL_{EC} was approximately half of the dialysis dose received (2.23 L/hr vs 4.4 L/hr). CL_{EC} in CKRT is sometimes estimated as the unbound fraction (f_u) multiplied by the Q_{ef} because only free solutes can pass through the CKRT filter. PIP has an f_u of ~70% (~30% protein binding), suggesting that CL_{EC} would be expected as ~70% of the Q_{ef}. The discrepancy between the observed and predicted CL_{EC} may exist because of decreased PIP availability for extracorporeal elimination due to intrinsic renal elimination. It also could be due to the limitations of using a predominantly diffusive, rather than convective, form of solute removal for CKRT CL,[1,18,23] as this patient was prescribed continuous veno-venous hemodialysis. This modality very effectively removes small molecules like oxalate, but less effectively clears molecules of middle MW (MW in the 500–50,000 Da range). With PIP's MW of 518 Da, it is considered a middle MW molecule despite being on the "small" end of the middle-MW range. Thus, PIP was perhaps less susceptible to CL_{EC} than would be expected from the prescribed effluent flow and degree of protein binding alone.

One additional change in PK/PD parameters in this patient over time is worth noting. PIP V_1 was likely elevated in the immediate postoperative period while the patient was off CKRT owing to the volume of fluids given immediately after the operation and the absence of much output (overall net fluid balance approximately +4.7 L during post CKRT period #1). This increase in V_1 did not appear to affect TA while the patient was off CKRT given the high percentage of *f*T > 1xMIC for all 3 off-CRKT periods. It is known that a larger V_d with a constant CL can increase half-life and thus time over MIC.[24,25]

Comparing these patient data directly to existing reports of PIP PK on CKRT is challenging in part because of differences in data reported and patients included. For example, Butragueño-Laiseca et al[11] reported only 3 patients with residual kidney function and did not explore the impact of residual diuresis. The case report by Tang-Girdwood et al[12] did not report UOP. While Thy et al[10] reported the impact of residual kidney function, they did not include UOP values for each patient or evaluations of UOPs above an oliguric level. In addition, the reports by Thy et al[10] and Butragueño-Laiseca et al[11] do not compare the CL on CKRT to the CL off CKRT for the patients in their studies, because their research is focused on PIP PK modeling.

Regardless, some comparisons regarding TA are apparent. The report by Tang Girdwood et al[12] found that CKRT provides a 50% increase in PIP CL while on CKRT vs off CKRT (3.0 L/hr vs 2.0 L/hr) in a 13-year-old, 42-kg patient with liver failure. This result is comparable to the 66% increase in PIP CL discussed in this article. Tang Girdwood et al[12] reported nearly 100% *f*T > 4xMIC for a MIC of 16 mg/L while on CKRT despite receiving a lower dose of 80 mg/kg every 8 hours while on CKRT and 48 mg/kg every 8 hours while off, which does not align with the 60% *f*T > 4xMIC for a MIC of 8 mg/L reported here. This discrepancy can be attributed to our patient's significant kidney function and high dialysis dose. Thy et al[10] simulated TA for a 15-kg patient on CKRT receiving

100 mg/kg of PTZ every 8 hours with a residual UOP of 0.5 mL/kg/hr and found approximately 75% *f*T > 4xMIC for a MIC of 8 mg/L. Butragueño-Laiseca et al[11] similarly reported PD TA of 78% fT > 4xMIC for a MIC of 8 mg/L in a simulated patient on CKRT weighing 10 to 30 kg and receiving 100 mg/kg of PTZ every 8 hours, though they could not explore the effect of residual kidney function. The TA for the patient in this study is lower, likely owing to both high-intensity CKRT and robust kidney function.

Because this was a single-patient case study, we cannot make broad generalizations regarding appropriate PTZ dosing in this patient population. That said, we simulated 3 dosing regimens that would achieve 100% *f*T > 4xMIC for on-circuit periods, assuming no change in CKRT or kidney CL: 110 mg/kg PTZ (98 mg/kg PIP) every 4 hours as a 30-minute infusion, 160 mg/kg PTZ (142 mg/kg PIP) every 6 hours as a 3-hour infusion, or 220 mg/kg/day PTZ (196 mg/kg PIP) as a continuous infusion. Concentration-time profiles for these simulated dosing regimens are available in Supplemental Figure A through C.

Limitations

This case study has limitations. Only 5 of the 22 concentrations were obtained when the patient was off CKRT. This is mainly because the patient was only off CKRT for short periods (mean of 9 hours vs mean of 38 hours on CKRT), but the paucity of data could result in less accurate estimates of PIP CL. Because this is a single-patient case report, we also cannot perform statistical inferential testing to examine the impact of patient- and CKRT-specific parameters in predicting PIP PK. We assume a fixed percentage of binding in the de Cock model used here, which may inaccurately represent the actual protein binding of PIP in this patient owing to his critical illness and fluctuating albumin levels. In addition, we did not collect urine or effluent PIP concentrations because the case study was subsumed under a parent study that only involved collection of scavenged opportunistic blood samples. Because piperacillin is known to have renal, hepatic, and extracorporeal clearance,[7,26,27] the absence of urine and effluent samples limited our ability to precisely quantify the contribution of each. Finally, because we do not have a validated assay for tazobactam at our institution, we could not perform tazobactam PK, which would have enriched this case report.

However, this report has strengths as well, especially owing to the unique nature of the patient case. To our knowledge, this is the first analysis of free PIP concentrations in a critically ill pediatric patient undergoing high-dose continuous dialysis. His significant intrinsic kidney function also adds to the novelty of the PK/PD results. The 17 free PIP concentrations available while the patient was on CKRT likely allowed for accurate estimates of PK parameters during those periods, as evidenced by the good fits of the observed concentrations while on CKRT.

Conclusions

This case report contributes valuable PIP PK data from a distinctive patient case to the sparse existing CKRT PK literature. We provide information about the potential effects of both the high dialysis dose and residual UOP above an oligoanuric level as is typically seen in children on CKRT. Clinical monitoring of free PIP concentrations may be warranted to better inform dosing in patients supported with CKRT, particularly given the discordance between dialysis dose and antibiotic elimination seen here. More frequent PIP dosing or prolonged or continuous infusions may be necessary to achieve stringent PD targets in this population, though more research is needed. Further analysis should be completed by using free PIP concentration data directly from critically ill pediatric patients receiving CKRT, including those with residual kidney function.

Article Information

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Ethical Approval and informed Consent. The authors assert that all procedures contributing to this work comply with the

ethical standards of the relevant national guidelines on human experimentation. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board who granted a waiver of informed consent for initial sample collection; thereafter, the patient's parent granted consent for publication of this case report.

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