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ARTICLE

Intraperitoneal pharmacokinetics of vancomycin in patients on automated peritoneal dialysis

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Abstract

It is unclear if the pharmacokinetics of vancomycin are the same during automated peritoneal dialysis (APD), where cycler exchanges may affect the systemic, peritoneal, and urinary disposition of drug. We conducted a prospective pharmacokinetic study evaluating the pharmacokinetics of vancomycin in plasma, dialysis fluid, and urine in peritonitis-negative patients on APD. Patients underwent four drug-free exchanges with 1.5% or 2.5% dextrose following the initial dwell period. Plasma, dialysis fluid, and urine was collected over the course of 7 days for pharmacokinetic analysis. Four patients completed the study with no adverse events. Following a median (range) dwell of 14.6 (14.2–17.6 h), the mean (±SD) observed maximum plasma concentration was 28.7 ± 4.9 mg/L with a mean bioavailability of 98.5 ± 1.4% prior to starting the cycler. The overall mean total plasma clearance estimated from study start to completion was 7.6 ± 1.2 ml/min. Mean total clearance during the dialytic exchange was 13.6 ± 4.9 ml/min. In patients with residual renal function, the mean vancomycin renal clearance was 3.1 ± 1.5 ml/min, representing 21.4%–58.9% of the overall total plasma clearance during the study period. Despite the small sample size, this pilot study suggests that the dwell time has important implications for systemic vancomycin exposure, time to therapeutic plasma concentration, and dosing. Dose is driven by dwell time, whereas the cycler determines the dosing interval. Rapid exchanges from APD will determine the frequency of dosing rather than the adequacy of absorption when vancomycin is given in the peritoneum.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Vancomycin dosing in patients with peritonitis during automated peritoneal dialysis (APD) is empiric and extrapolated from studies in patients on continuous ambulatory peritoneal dialysis (CAPD). Extrapolation of pharmacokinetic data from CAPD to APD may result in substantial under- or overdosing due to rapid exchanges and longer dwell times. The impact of residual renal function on vancomycin pharmacokinetics is also unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?
This study assessed the absorption and disposition of vancomycin following an intraperitoneal dose. Disposition of vancomycin was assessed in plasma, dialysis fluid, and urine.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Drug-dialysis fluid dwell times of up to 15 h achieves adequate therapeutic vancomycin concentrations in plasma. Rapid exchanges from APD increases vancomycin total systemic plasma clearance during the exchange period.
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Drug-dialysis fluid dwell time has direct influence on the systemic bioavailability and therapeutic concentration of vancomycin. Initial and maintenance vancomycin dosing regimens should account for the dwell time, dialytic and renal clearance, and microbial susceptibility.

INTRODUCTION

Home dialysis has seen a 12.5% increase among prevalent cases of patients with end-stage renal disease in the United States.[1] Among those on home dialysis, 85% of patients performed peritoneal dialysis (PD) with greater than half on PD using an automated cycler.[2] PD-associated peritonitis is a common complication of PD with an annual incidence of 26 episodes per 100 patients in the United States.[2] Approximately 37%–45% of PD-associated peritonitis cases are caused by gram-positive organisms with the remainder of cases due to gram-negative, culture-negative, polymicrobial, or from other sources.[2] Complications from peritonitis may be severe, and as a result one of the primary reasons for switch from PD to hemodialysis.[3,4]

The International Society for Peritoneal Dialysis (ISPD) recommends starting intraperitoneal antibiotics for PD-associated peritonitis with gram-positive and negative coverage with a dwell time for at least 6 h.[5] Empiric coverage with vancomycin is an option given its activity against gram-positive organisms, such as *Staphylococcus aureus*. In patients on peritoneal dialysis with PD-associated peritonitis, vancomycin is given as an intraperitoneal dose providing direct delivery of drug to the peritoneum. Vancomycin elimination occurs primarily through glomerular filtration such that advanced renal disease reduces drug clearance.

The recommended dose given by the ISPD is 15–30 mg/kg given every 5–7 days intermittently with therapeutic drug monitoring targeting trough serum levels of 15 mg/L. These dosing recommendations have been largely gathered from pharmacokinetic studies conducted in patients on continuous ambulatory peritoneal dialysis (CAPD) and extrapolated to patients on automated peritoneal dialysis (APD). There is limited evidence on the pharmacokinetics of vancomycin in APD. Compared to CAPD, APD uses longer dwell times and more frequent dialytic exchanges. These modality differences can lead to a difference in the proportion of drug delivered into systemic circulation from a drug-dialysis dwell following an intraperitoneal dose. With the addition of the automated cycler in APD, overall drug disposition may be impacted due to the frequent number of dialytic exchanges.[6]

We conducted a pilot observational pharmacokinetic study in patients on APD to characterize the vancomycin disposition in circulation, dialysis fluid, and urine. The study assessed the adequacy of vancomycin absorption following an extended drug-dialysis fluid dwell while estimating the pharmacokinetic parameters during the rapid exchanges.

MATERIALS AND METHODS

This study was approved by the Thomas Jefferson University Institutional Review Board and registered on clinicaltrials.gov (NCT03685747). The study was conducted in accordance to Good Clinical Practice standards

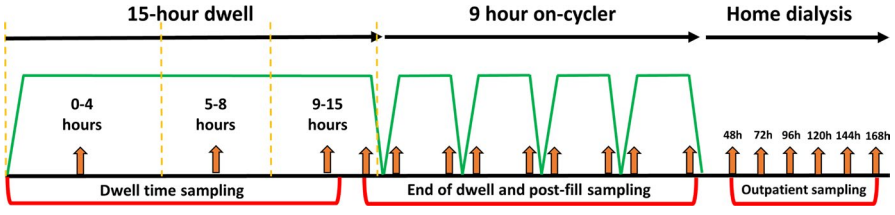

FIGURE 1 Study design and sampling schema

TABLE 1 Patient demographics and characteristics

	Age, years	Race	Sex	Weight, kg	Dose, mg	Creatinine clearance, ml/min/1.73 m^2	Time on peritoneal dialysis, months	Transport status	Home prescription
Subject 1	35	Black	F	99	2000	2.3	12	High average	4 Exchanges with 2.3 L 1.5% dextrose +1 L icodextrin for 9 h total
Subject 2	42	Asian	M	73	1500	0	9	High	6 Exchanges with 2 L 2.5% dextrose +1.2 L icodextrin for 9 h total
Subject 3	70	Asian	M	80	1500	6.5	16	High average	3 Exchanges with 1.8 L 1.5% dextrose for 8 h total
Subject 4	25	Asian	M	78	1500	12.9	14	Low average	5 Exchanges with 2.2 L 1.5% dextrose for 9.5 h total

and applicable federal and/or local regulatory requirements. All participants provided written informed consent prior to beginning the study.

Study population

Men or non-pregnant women between 18 and 85 years old on a stable APD regimen for greater than 3 months were eligible for the study. Individuals with an allergy or hypersensitivity to vancomycin or icodextrin, previous intraperitoneal antibiotic treatment or previous intravenous vancomycin within 2 months, active peritonitis infection, or had a hemoglobin less than 9 g/dl were excluded.

Study design, treatment, pharmacokinetic sampling, and bioanalysis

This was a prospective, single-site, open-label pharmacokinetic study in adult patients on APD. Enrolled participants were admitted into the Clinical Research Unit (CRU) at Thomas Jefferson University and remained overnight. On the first day in the CRU, participants received a one-time 20 mg/kg intraperitoneal vancomycin dose- rounded to the nearest 250 mg increment in one liter of icodextrin solution and allowed to dwell for at least 15 h. Plasma and dialysis fluid were sampled in collection windows at 0–4, 5–8, and 9–15 h postdose (Figure 1). Venous blood was sampled from a peripheral venous catheter and collected into BD Vacutainer tubes containing ethylenediaminetetraacetic acid. Synchronous drug-dialysis fluid (icodextrin) was sampled from the peritoneal dialysis catheter. Both matrices were immediately placed on ice after sampling. Patients underwent four APD exchanges with drug-free dextrose solution with dialysis fluid sampled during the drug-free dwell from the peritoneal dialysis catheter and drainage bag. Urine was collected in intervals ranging from 0–12 h, 12–24 h, and daily for up to 7 days in those with residual renal function. Urine was stored at room temperature with each collection interval and immediately placed into a refrigerator at the end of the interval during their time in the CRU and subsequent outpatient collections. Participants were discharged from the CRU after completing a full APD cycle and sampling. Plasma, dialysis fluid, and urine sampling continued from day 2 until the completion of the study (day 7).

For the outpatient portion of the study (study days 2–7), participants were asked to bring in a sample from their effluent collected in large volume bags from their daily exchange. A 24 h interval urine sample was also collected

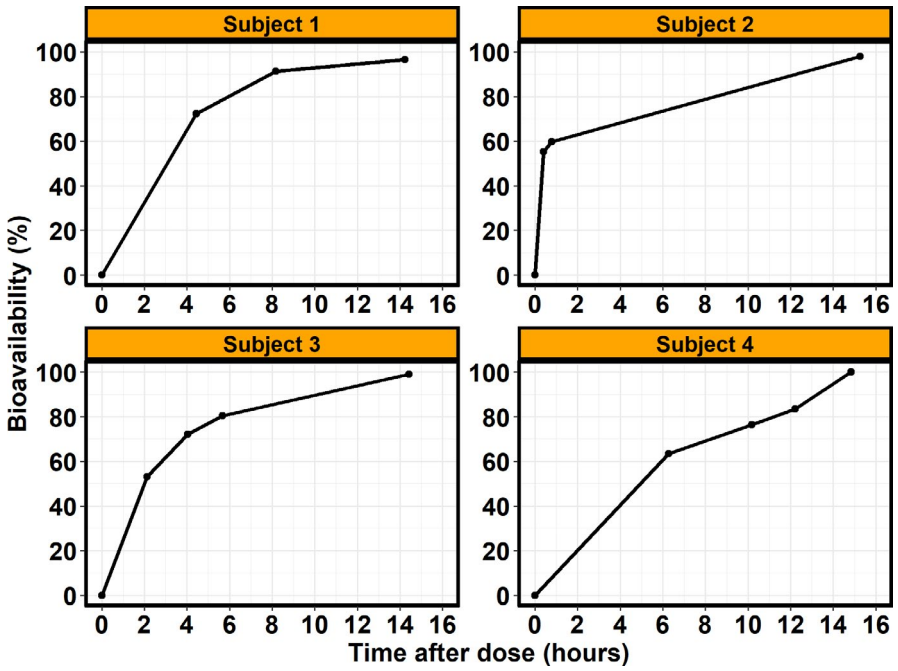

FIGURE 2 Bioavailability- represented as a percentage- over time during the drug-dialysis fluid dwell

for those who were non-anuric. With each study day that progressed, participants would bring effluent and urine collected from the previous day. A blood sample was also taken with each study day up until study day 7.

Whole blood, dialysis fluid (icodextrin and dextrose), and urine were centrifuged at 1200 *g* at 4°C. Plasma from whole blood and supernatant from the dialysis fluid and urine were placed in cryovials and stored at −80°C. Measurement of vancomycin in plasma, dialysis fluid (icodextrin and dextrose based), and urine was performed using the Roche Cobas serum/plasma immunoassay. Accuracy of assay results for dialysis fluid and urine as alternative sample matrices was verified beforehand.

Pharmacokinetic and statistical analysis

Plasma, dialysis fluid, and urine pharmacokinetic parameters were estimated using noncompartmental analysis and performed on Phoenix WinNonlin version 8.3 (Certara). Creatinine clearance was estimated from the 24 h urine collection and normalized to body surface area. Pharmacokinetic parameters estimated included the maximum concentration achieved after the drug-dialysis fluid dwell, area under the plasma concentration-time curve (AUC_{0-last}), total plasma clearance (CL/F), peritoneal transfer half-life ($t_{1/2absorption}$), systemic elimination half-life ($t_{1/2}$), and intraperitoneal bioavailability (F_{IP}). Total plasma clearance was estimated at two time periods with the first during the dialytic exchange period and the second for the overall duration of the study. CL/F during the dialytic exchange period was estimated based on the ratio of the amount of drug in plasma divided by the partial AUC during the entire exchange period. The peritoneal transfer half-life was estimated based on the decline observed during the drug-dialysis dwell and represents the transfer from the peritoneum into systemic circulation. Systemic elimination half-life was estimated based on the best-fit and included time points sampled during the terminal phase of elimination. F_{IP} was calculated using the equation $F_{IP} = D_{IP} - A_{D(t)} / D_{IP}$ where $A_{D(t)}$ represents the amount of drug in the drug-dialysis fluid sampled at time t and D_{IP} is the intraperitoneal dose. Volume of the drug-dialysis fluid during the dwell was assumed to be constant when estimating $A_{D(t)}$.

The dialytic clearance (CL_{APD}), representing vancomycin clearance during the drug-free cycler exchange, was estimated as the ratio of the cumulative amount recovered in the dialysis fluid over the partial AUC at the start of the first exchange to the time of the last exchange. Renal clearance (CL_R) was estimated based on the cumulative amount of drug recovered up until day 7 of the study divided by the AUC. Parameters were summarized descriptively and reported as mean and SDs.

RESULTS

Participant demographics

Four participants—three men and one woman—enrolled and completed the study (Table 1). The mean (±SD) age and weight were 43 (±19.3) years old and

TABLE 2 Vancomycin in plasma, dialysis fluid, and urine pharmacokinetic parameters following a single intraperitoneal dose

	T_{max}, h	C_{max}, mg/L	$AUC_{0\text{-last}}$, h × mg/L	CL/F, ml/min[a]	CL_R, ml/min	CL_{APD}, ml/min	CL/F, ml/min[b]	V/F, L	F, %	Plasma $t_{1/2}$, h	Peritoneal transfer half-life $t_{1/2absorption}$, h
Subject 1	13.8	34.4	3089.0	7.4	1.6	7.1	11.6	62.7	96.6	98.2	2.9
Subject 2	14.9	25.5	2635.8	5.5	-	6.5	6.5	62.8	98.0	132.4	3.3
Subject 3	14.0	23.8	2292.9	7.3	2.5	14.6	17.0	63.8	99.1	100.4	3.3
Subject 4	15.0	31.2	2341.9	8.6	5.1	16.2	19.2	49.2	99.8	66.0	4.0
Mean	14.4[c]	28.7	2589.9	7.2	3.1	11.1	13.6	59.6	98.4	99.3[c]	3.3[c]
SD	13.8 – 15.0[d]	4.9	365.6	1.3	1.5	4.3	4.9	6.9	1.4	66.0 – 99.3[d]	2.9 – 4.0[d]

Abbreviations: APD, automated peritoneal dialysis; AUC, area under the plasma concentration-time curve; CL/F, total plasma clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; F, bioavailability; $t_{1/2}$, systemic elimination half-life; $t_{1/2absorption}$, peritoneal transfer half-life; T_{max}, time to maximum concentration; V/F, volume of distribution.

[a]Represents the total plasma clearance for the duration of the study.

[b]Represents the total plasma clearance during the dialytic exchange period.

[c]Median values reported.

[d]Minimum and maximum range reported.

82.5 (±11.4) kg, respectively. The mean (±SD) time on peritoneal dialysis was 12.8 (±3.0) months. Three patients had remaining renal function with a mean (±SD) creatinine clearance corrected for body surface area of 7.2 (±4.4) ml/min/1.73 m^2. Only one participant received a 2000 mg dose (subject 1) whereas the remaining participants received 1500 mg. There were no safety issues or adverse events noted during the conduct of the study.

Vancomycin pharmacokinetics in plasma, dialysis fluid, and urine following a single intraperitoneal dose

Vancomycin was readily absorbed through the peritoneum and achieved a mean (±SD) 98.5 ± 7.8% bioavailability following a median (range) 14.6 (14.2–17.6) h drug-dialysis fluid dwell (Figure 2). Table 2 represents the absorption and elimination parameters estimated by noncompartmental analysis. The mean (±SD) maximum concentration achieved was 28.7 (±4.9) mg/L with a median peritoneal transfer half-life of 3.3 h (2.9–4.0). Figure 3 represents the plasma concentration-time curve with Figure 4 representing the decline of vancomycin over time during the drug-dialysis fluid dwell period. Figure 5 provides the vancomycin concentration-time curve in dialysis fluid during the entirety of the study with a zoom-in of the drug-dialysis dwell period. The median plasma elimination half-life was 99.3 h (66.0–132.4) with a mean (±SD) total plasma clearance of 7.2 (±1.3) ml/min. The average dialytic clearance (±SD) during the cycler-exchange was 11.1 (±4.3) ml/min with a median dwell time of 2.2 h (1.9–2.4) between each drug-free exchange among all participants. Three participants completed four cycler-exchanges, with the exception of one participant, who underwent three cycler-exchanges. The mean (±SD) vancomycin CL_R was 3.1 (±1.5) ml/min representing, on average, a cumulative 25% of the dose excreted in urine over the 7-day study period.

DISCUSSION

Intraperitoneal dosing of vancomycin provides direct localized contact to the site of infection in patients with PD-associated peritonitis. Current antibiotic dosing recommendations are extrapolated from studies in patients on CAPD. Although vancomycin remains standard for suspected and confirmed PD-peritonitis, the disposition of vancomycin in patients on APD following an intraperitoneal dose is unclear. In this study, a single 20 mg/kg intraperitoneal dose was given to peritonitis-negative

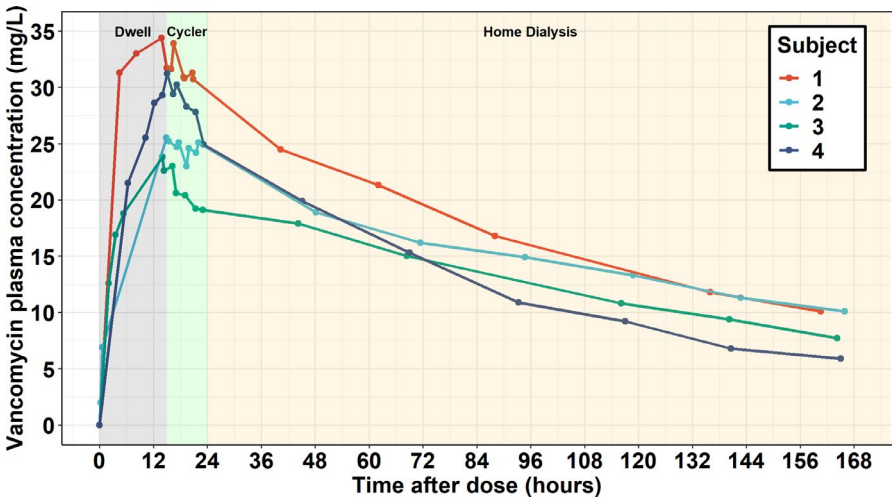

FIGURE 3 Individual plasma vancomycin concentration-time profiles following a single 20 mg/kg intraperitoneal dose in 1-liter of icodextrin

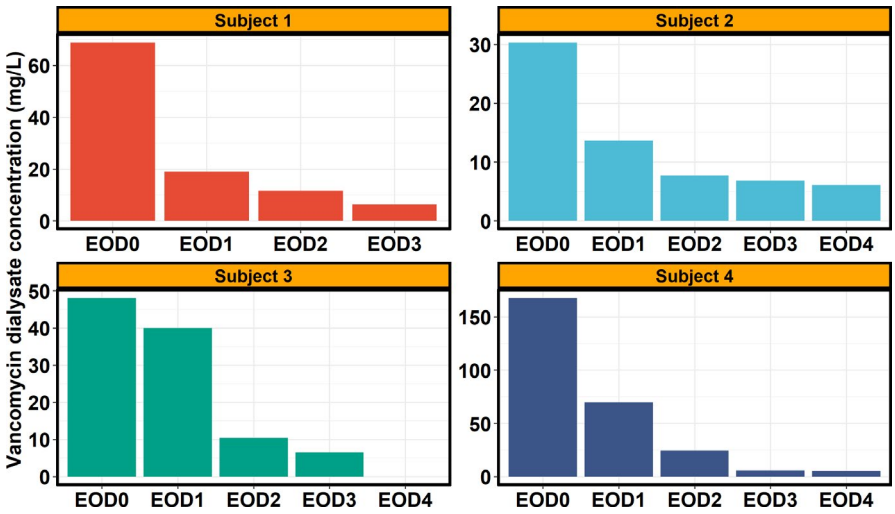

FIGURE 4 Vancomycin concentration in dialysis fluid during drug-free dialysis fluid exchange. The initial end of dwell (i.e., EOD0) represents the concentration of drug-dialysis fluid (icodextrin) whereas EOD1-4 represents the concentrations after each drug-free dwell and exchange. Subject 3 did not have detectable concentrations at EOD4. EOD, End of dwell

participants on APD. Plasma, dialysis fluid, and urine sampling was performed to assess the absorption and disposition of vancomycin during the dwell and exchange periods for up to 7 days.

We observed complete drug absorption from the peritoneum following a median 14.6 h drug-dialysis fluid dwell. Our observations align with previous studies conducted in patients on CAPD, which suggest a direct correlation between the dwell-time and bioavailability.[7] Moreover, the estimated median peritoneal transfer half-life between the peritoneum and systemic circulation was 3.3 h, which after five transfer half-lives, suggests that a 15 h dwell time is appropriate in order to allow complete drug transfer. Although the transfer half-life between plasma to the peritoneum was not estimated, other pharmacokinetic studies have observed an average of 2.8 h for vancomycin.[8]

The dialytic and renal clearances were also estimated in this study. During the exchange period immediately following the drug-dialysis fluid dwell, we observed a rapid decline in plasma vancomycin. In comparison to the overall 7-day total clearance, the mean total clearance during the dialytic exchange was substantially higher (13.6 vs. 7.2 ml/min). It should be noted that the total clearance estimated from the plasma profile from study start to the completion represents the overall vancomycin decline. This includes the decline from subsequent APD exchanges performed on an outpatient basis from study days 2 to 7. The increase in total clearance during the exchange period was a result of higher dialytic clearances, which accounted for 61%–86% of the total clearance during the exchange period. Total and dialytic clearances appear to trend higher in patients with greater residual renal function.

Our findings suggest that systemic vancomycin concentration is a function of the dwell time, as previously observed in patients on CAPD.[7] Increasing the dwell time during the day dwell allows for complete absorption of

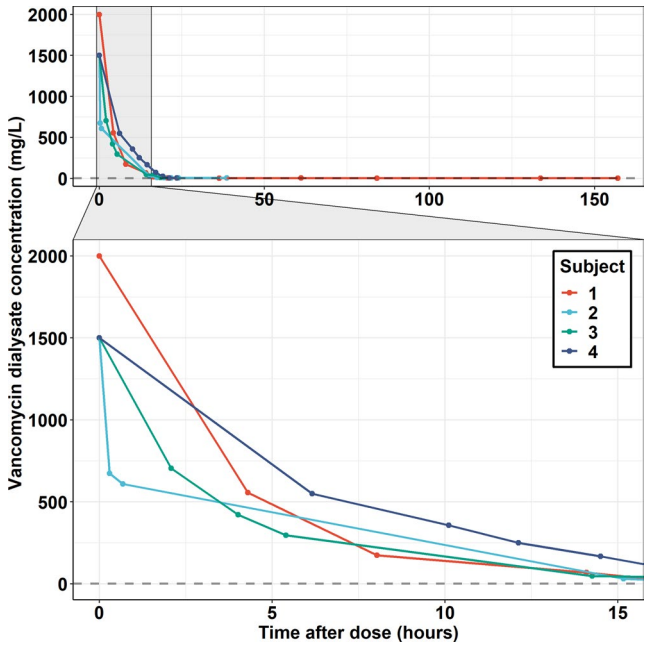

FIGURE 5 Individual dialysate vancomycin concentration-time profiles following a single 20 mg/kg intraperitoneal dose in 1-liter of icodextrin. The drug-dialysis dwell period was expanded to show the decline in concentration during this period. The horizontal dash line represents the limit of quantification (2 mg/L)

vancomycin prior to starting drug-free cycler exchanges. This forms the basis as to how much drug to give for a patient presenting with PD-peritonitis on APD. Selection of the initial dose should therefore focus on the pharmacokinetic parameters, such as the peritoneal transfer half-life, dwell time, and bioavailability. Contrary, rapid exchanges from the cycler determines how often drug is given. The pharmacokinetic parameters associated with dosing frequency in order to maintain therapeutic vancomycin levels is determined by the dialytic clearance, total systemic clearance, and elimination half-life. Therefore, assuming complete absorption from the peritoneum, rapid exchanges from APD will determine the frequency of dosing rather than the adequacy of absorption when vancomycin is given in the peritoneum.

The ISPD recommends vancomycin doses of 15–30 mg/kg every 5–7 days with a 15 mg/L therapeutic target trough plasma concentration.[5] We conducted a nonparametric superposition analysis using single-dose data from our four participants in order to predict plasma vancomycin profiles using various dosing regimens. Nonparametric superposition assumes each dose is independent from the other dose with the total clearance being the same with each dosing interval. Figure 6 plots the mean predicted concentrations after three additional doses following an initial loading dose (vertical facet) given every 3, 4, 5, or 7 days (horizontal facet). Based on the predictions, a 30 mg/kg load and maintenance dose given at the four dosing intervals produced mean concentrations that were associated with toxicity. Two regimens appear plausible in order to maintain mean levels at or above 15 mg/L while maintaining consistent peak values. This includes: (1) 15 mg/kg loading dose with a 15 mg/kg maintenance dose every 4 days, or (2) 20 mg/kg loading dose with a 10 mg/kg maintenance dose given every 3 days.

There are several limitations in our findings. Mainly, participants enrolled in this study did not have peritonitis. The rate of which vancomycin is absorbed is dependent on the peritoneal membrane.[6] During inflammatory peritonitis, the rate of absorption increases enhancing the rate of transfer from the peritoneum to systemic circulation. The enhanced rate of absorption may reduce the time required for complete absorption. Participants were also given a single intraperitoneal dose, which may not adequately capture the pharmacokinetics after multiple doses. The mismatch between the total overall clearance estimated throughout the duration of the study and the total clearance during the exchange portion may have likely resulted due to the variations in each patient's dialysis prescription (Table 1). The small sample size also limits the predictability of plasma concentrations after multiple doses.

Last, a majority of the participants in this study were non-anuric. As such, these predictions apply mainly to individuals with residual renal function and may not be generalizable to those who are anuric. Preserving residual renal function in patients who are non-anuric on PD is important for the maintenance of euvolemia. Vancomycin trough values greater than or equal to 15 mg/L and subsequent risk for nephrotoxicity have been frequently documented.[9] Current consensus guidelines recommend AUC-guided vancomycin dosing with an AUC/minimum inhibitory concentration (MIC) target of 400–600 mg × h/L in order to minimize the likelihood of acute kidney injury.[10] Although the current consensus applies to patients with suspected or confirmed methicillin-resistant *Staphylococcus aureus*, it is unclear if this index of exposure-response targeting is appropriate in patients on both modalities of peritoneal dialysis with PD-associated peritonitis. Moreover, optimal plasma or dialysis fluid sampling times remain unclear in practice. As target trough concentrations of 15 mg/L recommended by the ISPD is a surrogate marker for the AUC/MIC ratio, there is limited evidence of its use on microbiological cure in the peritoneum. Given that PD-associated peritonitis is a localized infection of the peritoneum, alternative methods of monitoring may have utility in order to determine the safety and efficacy

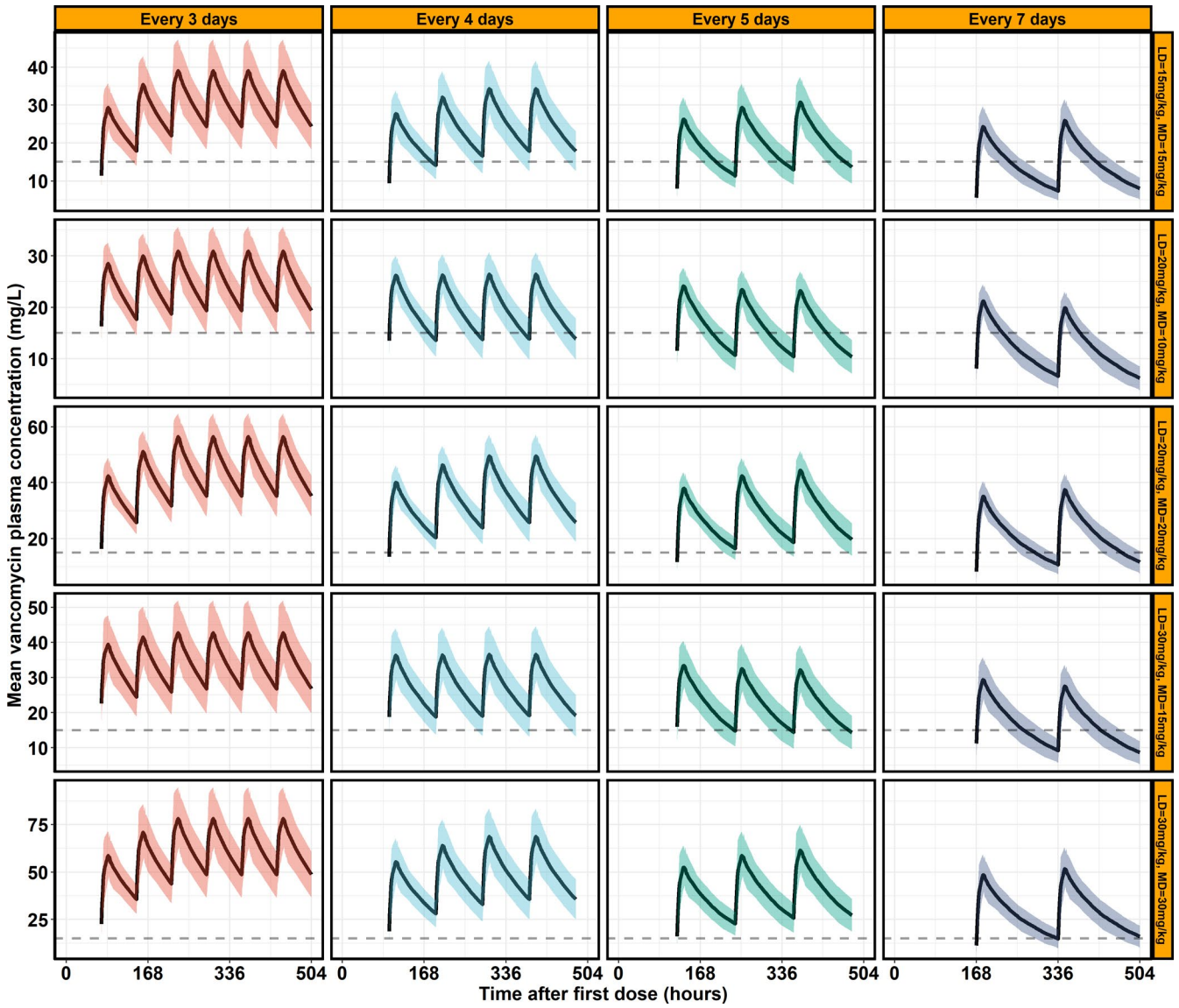

FIGURE 6 Nonparametric superposition predictions for plasma concentration-time profiles following five loading and maintenance dosing scenarios (vertical facet) and frequencies (horizontal facet). Predictions used single-dose data established from the four patients in this study assuming complete drug absorption during the day dwell. The solid line represents mean concentrations (from the 4 patients) with the shaded regions representing the ±SD

of vancomycin in this population. This includes concentration monitoring of dialysis fluid during peritonitis and establishing correlates for its microbiological efficacy at the site of infection.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

E.L. and J.Z. wrote the manuscript. E.L. and Y.T.K. designed the research. J.Z., W.K.K., and E.L. performed the research. E.L., Y.T.K., B.P., and J.Z. analyzed the data. D.F.S. contributed new reagents/analytical tools.

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