PHARMACOKINETICS OF INTRAPERITONEAL CEFALOTHIN AND CEFAZOLIN IN PATIENTS BEING TREATED FOR PERITONEAL DIALYSIS-ASSOCIATED PERITONITIS

Darren M. Roberts,^{1,2} Dwarakanathan Ranganathan,^{3,*} Steven C. Wallis,¹ Julie M. Varghese,¹ Adrian Kark,³ Jeffrey Lipman,^{1,4} and Jason A. Roberts^{1,4,5,*}

Burns, Trauma & Critical Care Research Centre,¹ School of Medicine, The University of Queensland, Butterfield Street, Herston, Queensland, Australia; Medical School,² Australian National University, Acton, ACT, Australia; Department of Renal Medicine,³ Royal Brisbane & Women's Hospital, Butterfield Street, Herston, Queensland, Australia; Department of Intensive Care Medicine,⁴ Royal Brisbane & Women's Hospital, Butterfield Street, Herston, Queensland, Australia; and Pharmacy Department,⁵ Royal Brisbane & Women's Hospital, Butterfield Street, Herston, Queensland, Australia

◆ **Background:** The standard treatment of peritoneal dialysis (PD)-associated peritonitis (PD-peritonitis) is intraperitoneal (IP) administration of antibiotics. Only limited data on the pharmacokinetics and appropriateness of contemporary dose recommendations of IP cefalothin and cefazolin exist. The aim of this study was to describe the pharmacokinetics of IP cefalothin and cefazolin in patients treated for PD-peritonitis.

◆ **Methods:** As per international guidelines, IP cefalothin or cefazolin 15 mg/kg once daily was dosed with gentamicin in a 6-hour dwell to patients with PD-peritonitis during routine care. Serial plasma and PD effluent samples were collected over the first 24 hours of therapy. Antibiotic concentrations were quantified using a validated chromatographic method with pharmacokinetic analysis performed using a non-compartmental approach.

◆ **Results:** Nineteen patients were included (cefalothin $n = 8$, cefazolin $n = 11$). The median bioavailability for both antibiotics exceeded 92%, but other pharmacokinetic parameters varied markedly between antibiotics. Both antibiotics achieved high PD effluent concentrations throughout the antibiotic dwell. Cefazolin had a smaller volume of distribution compared with cefalothin (14 vs 40 L, $p = 0.003$). The median trough total plasma antibiotic concentration for cefazolin and cefalothin during the dwell differed (plasma 56 vs 13 mg/L, $p < 0.0001$) despite a similar concentration in PD effluent (37 vs 38 mg/L, $p = 0.58$). Lower antibiotic concentrations were noted during PD dwells not containing antibiotic, particularly cefalothin, which was frequently undetectable in plasma and PD effluent. The median duration that the unbound antibiotic concentration was above the minimum inhibitory concentration (MIC) was approximately 13% (plasma) and 25% (IP) for cefalothin, and 100% (plasma and IP) for cefazolin, of the dosing interval.

◆ **Conclusions:** When IP cefalothin or cefazolin is allowed to dwell for 6 hours, sufficient PD effluent concentrations are present for common pathogens during this time. However, with once-daily IP dosing, in contrast to cefazolin, there is a risk of subtherapeutic plasma and PD effluent cefalothin concentrations, so more frequent dosing may be required.

KEY WORDS: Antibiotic; cephalosporin; dialysis; infection; peritonitis; pharmacokinetics.

Peritoneal dialysis (PD) is a widely used form of renal replacement therapy for patients with end stage renal disease (ESRD). A possible complication that causes pain and systemic illness and may require hospital admission is PD-associated peritonitis (PD-peritonitis) (1).

Standard treatment of PD-peritonitis includes intraperitoneal (IP) administration of antibiotics. The International Society for Peritoneal Dialysis (ISPD)-recommended first-line empiric antibiotics include first-generation cephalosporins, in particular cefalothin or cefazolin (2). Either of these first-generation cephalosporins is admixed in a bag of PD fluid with gentamicin or ceftazidime and then instilled intraperitoneally for 6 hours. This is repeated once daily for approximately 14 days; if the infecting organism is resistant to this combination then different antibiotics may be required.

Cephalosporins are bactericidal when their concentration exceeds the minimum inhibitory concentration (MIC) of the bacteria, which is usually 1 – 8 mg/L (3,4), known as time-dependent killing. The concentration of antibiotic at the site of infection (the peritoneal membrane) is most relevant for bacterial killing; however, systemic illness can occur that may be due in part to bacteremia, so knowledge of plasma pharmacokinetics is also of significant interest. Subtherapeutic antibiotic concentrations are likely to predispose to treatment failure and the emergence of bacterial resistance. Principles regarding the pharmacokinetics of IP antibiotics are outlined in the online supplement.

Because cephalosporin clearance is proportional to kidney function, the half-life will be prolonged in patients with ESRD,

Correspondence to: Darren Roberts, Burns, Trauma & Critical Care Research Centre, School of Medicine, The University of Queensland, Butterfield Street, Herston, Queensland 4029, Australia.

darren.roberts@uq.edu.au

Received 13 January 2015; accepted 23 June 2015.

Supplemental material available at www.pdconnect.com

Perit Dial Int 2016; 36(4):415–420 epub ahead of print: 13 Jan 2016
<http://dx.doi.org/10.3747/pdi.2015.00008>

* Dwarakanathan Ranganathan and Jason Roberts are joint-senior authors.

This single copy is for your personal, non-commercial use only.
For permission to reprint multiple copies or to order presentation-ready
copies for distribution, contact Multimed Inc. at marketing@multi-med.com

the extent of this prolongation being dependent on residual renal function and dialytic clearance. Further, because more than 30% of cefalothin clearance is by metabolism (5–7), its half-life is anticipated to be shorter than that of cefazolin. Despite this, however, ISPD dosing recommendations for treating PD-peritonitis are identical for cefalothin and cefazolin (2).

Existing cephalosporin pharmacokinetic data in ESRD are limited because they were performed in a small number of volunteers who were not receiving PD, or without PD-peritonitis limiting generalizability (6–11). In addition, few studies have reported IP antibiotic concentrations or evaluated the effect of antibiotic-free PD exchanges. Finally, many were performed over 30 years ago, when antibiotic concentrations were determined using the method of bacterial inhibition (7–9,12), which is error-prone compared with direct chromatographic methods. So the extent to which the current dosing regimen optimizes bacterial kill is not known. This is in contrast to vancomycin and gentamicin therapy where dosing is usually guided by plasma concentration monitoring (13).

Therefore, there is considerable uncertainty regarding the IP and plasma concentration-time profile of cefalothin and cefazolin in patients with PD-peritonitis, in particular cefalothin, when prescribed using the ISPD protocol. The aim of this study is to determine the IP and systemic pharmacokinetics of cefalothin and cefazolin in patients treated for PD peritonitis. We also sought to determine whether the observed plasma and PD effluent concentrations achieved exposures associated with maximal antibacterial activity.

SUBJECTS AND METHODS

PATIENT POPULATION

The protocol for this study has been published previously (14) along with the results for gentamicin (15). The present study extends the previous study, involving patients also administered a first-generation cephalosporin.

In brief, this prospective observational pharmacokinetic study involved PD patients who presented with clinical signs and symptoms of PD-peritonitis (abdominal pain, nausea, vomiting, diarrhea, fever, or cloudy effluent) and were treated with IP cephalosporin therapy. Patients were eligible if at least 18 years old and maintained on continuous ambulatory PD (CAPD) or automated PD (APD) for at least 1 month. The clinical diagnosis was confirmed by PD effluent cell count, differential, and culture.

On hospital admission, APD patients were switched to CAPD during the acute phase of peritonitis. All patients received 4 exchanges per day with dialysate volumes of 2 L per exchange. Peritoneal dialysis solutions used were either Dianeal (1.5% or 2.5% glucose; Baxter Healthcare, Deerfield, IL, USA) or stay*safe (1.5% or 2.3% glucose; Fresenius Medical Care, Bad Homburg, Germany). For some patients, Extraneal (7.5% icodextrin; Baxter Healthcare, Deerfield, IL, USA) was used for a long dwell; however, none of these patients had IP antibiotics added to the Extraneal dialysis fluid.

The study included patients with differing peritoneal membrane transporter status (low-average, high-average, and high transporters) and residual renal function (anuric [< 50 mL/24 h] and non-anuric). Patients who had received a course of IP antibiotics in the preceding 2 weeks were not eligible for the study.

This study was performed in a 986-bed tertiary referral hospital. Ethics approval was obtained from the Royal Brisbane and Women's Hospital Human Research and Ethics Committees (HREC/08/QRBW/8) and the Medical Research Ethics Committee of the University of Queensland (2009000673). It adhered to the Declaration of Helsinki and written informed consent was obtained from all participants. The trial was also registered on the Australian New Zealand Clinical Trial Registry (ANZCTR N12609000446268).

STUDY PROTOCOL

Antibiotics were prescribed as per the local peritonitis treatment protocol and based on actual body weight. Consistent with the ISPD guidelines, 15 mg/kg of cefalothin or cefazolin (dissolved in 10 mL water and rounded up to the nearest 5–50 mg dosage), according to physician preference, and gentamicin were added to a 2-L dialysate bag which was well shaken. This admixed bag was infused into the peritoneal cavity and allowed to dwell for 6 hours. Serial blood samples were collected from an indwelling peripheral intravenous cannula at 1, 3, 6, 7 and 24 hours after the IP administration of the antibiotic-containing bag. Effluent samples were collected at 3 and 6 hours and at the end of the 3 subsequent dialysis exchanges up to 24 hours after the first IP antibiotic dose. Samples were stored at -80°C until assayed. A 24-hour urine collection was performed at the start of the study to determine patients' residual renal function. Urinary creatinine clearance (CrCL) over 24 hours, corrected for body surface area, was calculated according to a standard equation as reported previously (15).

Clinical and demographic data were also collected for each patient, including their peritoneal membrane transporter status as classified by the standardized peritoneal equilibration test (16).

ANTIBIOTIC ASSAY

Cefazolin and cefalothin were measured by UHPLC-MS/MS (17). Depending on the matrix measured, the lower limit of quantitation for cefazolin in plasma and PD effluent was 0.1–1.0 mg/L and cefalothin was 0.2–1 mg/L.

PHARMACOKINETIC ANALYSIS AND INTERPRETATION

A noncompartmental pharmacokinetic approach was used to analyze the data, as described previously (15). Concentrations less than the lower limit of quantification were considered zero.

The plasma elimination rate constant, k_{el} , was calculated using the negative slope of the log-transformed concentration-time

data from plasma samples between 6 and 24 hours. The plasma elimination half-life, $t_{1/2,el}$, was calculated by

$$t_{1/2,el} = 0.693/k_{el}$$

The rate constant for distribution of the drug from the peritoneal cavity, $k_{pc,0-6}$, was calculated by using the negative slope of the log-transformed concentration-time data from plasma samples between 0 and 6 hours. The distribution half-life from the peritoneal cavity between 0 and 6 hours, $t_{1/2,pc,0-6}$, was calculated by

$$t_{1/2,pc,0-6} = 0.693/k_{pc,0-6}$$

The area under the plasma concentration time curve from 0 to infinity ($AUC_{plasma,0-\infty}$) was calculated using the linear trapezoidal rule between 0 and 24 hours, and then dividing the last plasma concentration at time 24 hours by k_{el} .

$F = (\text{dose added to dialysate} - \text{amount in effluent}) / \text{dose added to dialysate}$

Total clearance (CL_{total}) is determined by

$$CL_{total} = (F \times \text{Dose}) / AUC_{plasma,0-\infty}$$

Volume of distribution (V_d) was calculated as

$$V_d = CL_{plasma\ 0-24} / k_{el}$$

Where F is bioavailability (fraction of IP dose absorbed)

The plasma antibiotic concentration was interpreted relative to the MIC of bacteria considered susceptible to these antibiotics, which ranges from 1–8 mg/L according to EUCAST MIC breakpoints (6).

STATISTICAL ANALYSES

Continuous variables are expressed as median (interquartile range), and the statistical difference between antibiotics was determined using the Mann-Whitney test. Proportions were compared using the Fisher's exact (2 data pairs) or chi-square (more than 2 data pairs) tests. A p value of 0.05 was considered statistically significant. All regressions and statistics were conducted using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

Nineteen patients were included in this study (cefalothin $n = 8$ and cefazolin $n = 11$). Baseline demographic and clinical details are shown in Table 1. There were no statistically significant differences between patients receiving cefalothin and cefazolin in terms of age, weight, antibiotic dose, urine output, or CrCL.

Data on antibiotic concentrations and pharmacokinetics are listed in Table 2. The bioavailability and rate of distribution from the peritoneal space ($k_{pc,0-6}$ and $t_{1/2,pc}$) were similar for each antibiotic. The median antibiotic concentration in the PD effluent in the initial effluent sample exceeded 35 mg/L for each antibiotic. However, in subsequent PD effluent samples a significant difference was noted, where cefalothin was seldom detected whereas the cefazolin concentration exceeded 10 mg/L for the entire 24 hours. Plasma clearance did not differ between anuric and non-anuric patients for cefazolin, the antibiotic with the most numerous data ($p = 0.53$).

The maximum total plasma concentration of cefazolin was significantly higher than that of cefalothin, reflecting

TABLE 1
Demographic and Clinical Variables^a

	Cefalothin ($n=8$)	Cefazolin ($n=11$)	<i>P</i> value
Age (years)	53 (44–67)	71 (49–79)	0.17
Sex (male:female)	4:4	5:6	1.0
Weight (kg)	75.5 (69.5–87.5)	77.5 (66.3–90.5)	0.82
IP dose (mg; median, IQR)	1,065 (1,025–1,325) ^c	1,200 (1,000–1,373)	>0.99
Urine output			
Anuric ^b (n)	3	5	1.0
Non-anuric, (mL/24 h)	179 (175–447)	731 (227–1,188)	0.42
Creatinine clearance (mL/min)	1 (0–2)	0 (0–3)	0.89
Peritoneal membrane transporter status			
Low-average	2	2	
High-average	4	5	0.86
High	2	4	

IP = intraperitoneal; IQR = interquartile range.

^a Median and IQR shown and compared using Mann-Whitney test, unless otherwise specified.

^b Defined as urine output <50 mL/24 hours

^c $n=7$

TABLE 2
Antibiotic Concentrations and Pharmacokinetic Parameters

Parameter ^a	Cefalothin (n=8)	Cefazolin (n=11)	P value
F	0.92 (0.86–0.99)	0.93 (0.86–0.94)	0.98
F _u (%)	51.0 (44.9–54.9)	36.1 (33.7–42.4)	0.02
C _{max, plasma 0–6} (mg/L)	23.2 (21.7–24.4)	62.4 (55.7–76.5)	0.001
C _{min, plasma, 6} (mg/L)	13.3 (11.0–15.8)	56.3 (43.8–69.4) ^b	<0.0001
C _{min, plasma, 24} (mg/L)	0.0 (0.0–0.1)	40.6 (35.6–49.1) ^b	<0.0001
AUC _{plasma 0–6} (mg·h/L)	91.5 (67.0–102.4)	342.6 (275.4–426.6)	<0.0001
AUC _{plasma 0–infinity} (mg·h/L)	117.0 (92.6–160.9)	1,045.8 (799.9–3108.0)	0.0001
Concentration in PD effluent (mg/L)			
6 hours	38.4 (11.1–45.3)	37.4 (31.7–59.5)	0.58
12 hours	0.0 (0.0–1.3)	19.4 (16.8–22.8) ^b	0.0007
18 hours	0.0 (0.0–0.0)	19.0 (12.1–23.0) ^b	<0.0001
24 hours	0.0 (0.0–0.0)	14.4 (12.6–20.4) ^b	<0.0001
k _{el} (h ⁻¹)	0.23 (0.19–0.27)	0.06 (0.03–0.09)	0.0002
t _{1/2,el} (h)	3.01 (2.64–3.72)	11.43 (7.39–28.15)	0.0002
k _{pc,0–6} (h ⁻¹)	0.40 (0.33–0.49)	0.27 (0.21–0.30)	0.07
t _{1/2,pc,0–6} (h)	1.8 (1.4–2.1)	2.6 (2.3–3.4)	0.07
Vd (L)	39.69 (30.22–46.95)	14.41 (12.92–16.69)	0.003
CL _{total} (L/h)	10.72 (5.57–13.28)	0.99 (0.41–1.33)	0.0001

F = fraction of IP dose absorbed (bioavailability); F_u = fraction of antibiotic that is unbound to plasma proteins; C_{max, plasma 0–6} = peak plasma concentration in first 6 hours post-IP administration; C_{min, plasma, 6} = trough plasma concentration at 6 hours; C_{min, plasma, 24} = trough plasma concentration at 24 hours; AUC_{plasma 0–6} = area under the plasma concentration time curve between 0 and 6 hours; AUC_{plasma 0–24} = area under the plasma concentration time curve between 0 and 24 hours; PD = peritoneal dialysis; k_{el} = plasma elimination rate constant; t_{1/2,el} = plasma elimination half-life; k_{pc,0–6} = rate constant for distribution of drug from the peritoneal cavity between 0 and 6 hours; t_{1/2,pc,0–6} = distribution half-life in the peritoneal cavity between 0 and 6 hours; Vd = volume of distribution; CL_{total} = total clearance from the systemic circulation; IP = intraperitoneal.

^a All values are reported as median (interquartile range) and based on the total concentration

^b n=10

cefazolin's smaller volume of distribution. The lower plasma clearance of cefazolin resulted in a higher area under the concentration-time curve (AUC) compared with cefalothin. This reflects the higher initial total plasma concentration and prolonged elimination half-life of cefazolin compared with cefalothin. Given the shorter plasma elimination half-life of cefalothin, it was undetectable in the plasma of 7 (88%) patients 24 hours after IP cefalothin, in contrast to cefazolin where the median total concentration was 40.6 mg/L (free concentration 15.9 mg/L).

Following the initial antibiotic-admixed IP dwell, the concentration-time profile for the unbound (free) plasma and PD antibiotic concentrations were similar, suggesting equilibrium, Figure 1.

The unbound plasma and PD cephalosporin concentrations were compared to an MIC of 8 mg/L. For cefalothin, the unbound plasma concentration exceeded the MIC in 7 of 8 patients at 1 and 3 hours, in 2 of 8 patients at 6 hours, and in none at 7 and 24 hours. The cefalothin concentration in the PD effluent exceeded the MIC in 7 of 8 patients at 6 hours, then no patients at 12, 18 or 24 hours. In contrast, for cefazolin, both the unbound plasma and PD concentration were below the upper MIC for only 1 patient at each time point (this patient had the highest glomerular filtration rate (GFR), at 14 mL/min,

Figure 1 — Median unbound (free) plasma and peritoneal effluent concentrations following a single IP administration of cefalothin or cefazolin. IP = intraperitoneal; MIC = minimum inhibitory concentration.

and urine output of 3.5 L/day), and, in another, the PD concentration was 7.3 mg/L at 24 hours. Overall, the median duration that the unbound antibiotic concentration remained above the MIC was approximately 13% (plasma) and 25% (IP) for cefalothin, and 100% (both plasma and IP) for cefazolin, of the dosing interval.

DISCUSSION

Intraperitoneal administration of cefalothin and cefazolin produces a high initial IP and plasma concentration but this is only sustained in the case of cefazolin. In contrast, following the first IP dwell, cefalothin was undetectable in the IP space, which is the site of infection, whereas the concentration of cefazolin remained elevated and exceeded the MIC of relevant bacteria for the dosing interval in 91% of patients. The variability in disposition between these 2 antibiotics reflects their differences in pharmacokinetics, notably the larger volume of distribution and shorter elimination half-life of cefalothin. This has implications for the once-daily IP dosing regimen which is commonly used, whereby it may be insufficient in the case of cefalothin or potentially excessive in the case of cefazolin. Further clinical studies may be useful to determine whether these findings influence clinical outcomes.

INTRAPERITONEAL CEFAZOLIN

The half-life of cefazolin in our patients was 11.4 hours, which is long compared with the half-life in the context of normal renal function, < 2 hours (18,19). However, the half-life in anephric patients in the absence of renal replacement therapy is 42 hours (19), allowing less frequent administration (20). The shorter half-life during PD compared with anephric patients reflects clearance by PD exchanges, and, potentially, residual renal function. Two studies noted that cefazolin had an IP bioavailability of 70 – 80% and elimination half-life of 30 – 40 hours in patients without PD-peritonitis (10,11), compared with 93% and 11 hours, respectively, in our patients with PD-peritonitis. This difference probably relates to increased absorption in the presence of an inflamed peritoneum and PD exchanges. A multiple-dose study noted an elimination half-life for cefazolin of 16.9 hours in patients with PD-peritonitis and accumulation over subsequent days with continuous IP administration (21).

INTRAPERITONEAL CEFALOTHIN

Data about the pharmacokinetics of cefalothin in patients with ESRD are more complicated. The elimination half-life in patients with advanced chronic kidney disease is 2 – 3 hours (6–8), consistent with our results, compared with less than 1 hour in patients with normal renal function (5–7,9,22,23). However, a study noted a biphasic elimination profile (half-life 3.0 – 4.6 hours, then 16 – 19 hours [9,22]), while another noted a half-life of 18 hours after multiple intravenous and/or intramuscular doses (9). The different results may relate to these studies being performed over 25 years ago when antibiotic concentrations were determined using bacterial inhibition, so the prolonged elimination phase observed may relate to an active metabolite (7,22,23). The sensitivity of bacteria associated with PD-peritonitis to this metabolite is unknown. However, the plasma and effluent concentrations following IP cefalothin determined by this assay were similar to those observed in our study (8).

The total plasma cefalothin concentration was greater than 20 mg/L (whereby the free concentration would exceed the MIC) for 6 hours after IP administration of 1 g cefalothin to 2 patients with PD-peritonitis (8); we observed lower concentrations, see Figure 1. A study noted that PD decreased the cefalothin area-under-the-curve following intravenous administration, but the extent to which this occurred was not quantified (12). Another study noted that the elimination half-life in patients administered intravenous cefalothin and receiving PD exchanges (without admixed antibiotics) was 3 – 5.1 hours (8,21), which is similar to that noted without PD exchanges.

IMPLICATIONS OF THESE DATA

Marked differences in the pharmacokinetics of IP cefazolin and cefalothin were noted in this study, yet the ISPD guidelines recommend an identical dosing regimen (2). These findings highlight a potentially increased risk of therapeutic failure from cefalothin, compared with cefazolin. We are not aware of any head-to-head studies comparing cefazolin and cefalothin, and, perhaps fortunately, in recent years cefazolin is used more commonly than cefalothin (24–27). Nevertheless, our research may question the paradigm of comparing outcomes based solely on type of antibiotic (25) without considering dosing regimen. Suggestions for future research in this field, including evaluation of more frequent dosing of cefalothin and the effect of residual renal function, are outlined in the online supplement.

STRENGTHS AND LIMITATIONS

One of the strengths of this study is that it was performed prospectively using a predetermined regimen in patients with PD-peritonitis treated with a clinically relevant antibiotic regimen, and with complete data collection. Therefore, data are anticipated to be accurate and generally applicable. Antibiotic concentrations were measured using a validated specific assay, although a potential limitation of this may be that we were unable to screen for the presence of a metabolite of cefalothin. Data interpretation was limited to cefalothin and cefazolin pharmacokinetics that are reproducible and clinically relevant, but to limit inconvenience to patients, the elimination phase was determined using only 2 samples.

Some subanalyses could not be performed due to the small number of patients, for example the influence of peritoneal membrane transporter status and residual renal function on cephalosporin pharmacokinetics. However, in the case of transporter status, bioavailability exceeded 90% in each patient, so this did not appear to have a major effect. Further, there was relatively limited variability in pharmacokinetics within the group administered an individual antibiotic. Therefore, although the study was relatively small, the consistency of the results suggests that the accuracy of the predicted data may not be improved by increasing the sample size.

This is a single-dose study following the initial dose, so the effects of repeated doses on cephalosporin concentrations, including the risk of accumulation, are not determined.

CONCLUSION

Intraperitoneal cefazolin for the treatment of PD-peritonitis appears to result in a concentration-time profile that optimizes bacterial kill, in comparison with IP cefalothin, in which the IP and plasma concentrations were frequently noted to be undetectable. Therefore, cefazolin may be the preferred treatment when a first-generation cephalosporin is to be given once daily in the treatment of PD-peritonitis. Inter-individual variability appeared to be limited, but the effect of residual renal function may not have been fully explored in this study, so future studies need to address this. Further, because the trough (pre-dose) concentration was substantially elevated, there may be a risk of cefazolin accumulation over a 14-day treatment course. In both cases, monitoring the concentration of these antibiotics may be useful for ensuring that a therapeutic concentration is achieved.

ACKNOWLEDGMENTS

The authors thank the medical and nursing staff at the Department of Renal Medicine at the Royal Brisbane and Women's Hospital for their help in completing this study. This study is partly funded by an unrestricted grant from Royal Brisbane & Women's Hospital Research Foundation. JR is supported by a Career Development Fellowship from the National Health and Medical Research Council of Australia (APP1048652).

DISCLOSURES

The results presented in this paper have not been published previously in whole or part, except in abstract format as a poster at 'Kidney Week 2014, American Society of Nephrology,' Philadelphia, USA. The authors have no financial conflicts of interest to declare.

REFERENCES

1. Brown F, Gulyani A, Dent H, Hurst K, McDonald S. Chapter 6. Peritoneal dialysis. *ANZDATA Registry 2011 Report*. [Online.] Available at: http://www.anzdata.org.au/v1/report_2011.html; 2011.
2. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, *et al.* Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010; 30:393–423.
3. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; 26:1–10; quiz 11–2.
4. Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an *in vitro* pharmacokinetic model. *Antimicrob Agents Chemother* 1994; 38:931–6.
5. Nightingale CH, Greene DS, Quintiliani R. Pharmacokinetics and clinical use of cephalosporin antibiotics. *J Pharm Sci* 1975; 64:1899–926.
6. Kunin CM, Atuk N. Excretion of cephaloridine and cephalothin in patients with renal impairment. *N Engl J Med* 1966; 274:654–6.
7. Kirby WM, De Maine JB, Serrill WS. Pharmacokinetics of the cephalosporins in healthy volunteers and uremic patients. *Postgrad Med J* 1971; 47(Suppl):41–6.
8. Imada A, Itagaki N, Hasegawa H, Horiuchi A. Comparative study of the pharmacokinetics of various beta-lactams after intravenous and intraperitoneal administration in patients undergoing continuous ambulatory peritoneal dialysis. *Drugs* 1988; 35(Suppl 2):82–7.
9. Kabins SA, Cohen S. Cephalothin serum levels in the azotemic patient. *Antimicrob Agents Chemother (Bethesda)* 1964; 10:207–14.
10. Low CL, Gopalakrishna K, Lye WC. Pharmacokinetics of once daily intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. *J Am Soc Nephrol* 2000; 11:1117–21.
11. Manley HJ, Bailie GR, Asher RD, Eisele G, Frye RF. Pharmacokinetics of intermittent intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 1999; 19:65–70.
12. Perkins RL, Smith EJ, Saslaw S. Cephalothin and cephaloridine: comparative pharmacodynamics in chronic uremia. *Am J Med Sci* 1969; 257:116–24.
13. Johnson DW. Do antibiotic levels need to be followed in treating peritoneal dialysis-associated peritonitis? *Semin Dial* 2011; 24:445–6.
14. Ranganathan D, Varghese JM, Fassett RG, Lipman J, D'Intini V, Healy H, *et al.* Optimising intraperitoneal gentamicin dosing in peritoneal dialysis patients with peritonitis (GIPD) study. *BMC Nephrol* 2009; 10:42.
15. Varghese JM, Roberts JA, Wallis SC, Boots RJ, Healy H, Fassett RG, *et al.* Pharmacokinetics of intraperitoneal gentamicin in peritoneal dialysis patients with peritonitis (GIPD study). *Clin J Am Soc Nephrol* 2012; 7:1249–56.
16. Twardowski ZJ, Nolph KO, Khanna R, Prowant BF, Ryan LP, Moore HL, *et al.* Peritoneal equilibration test. *Perit Dial Bull* 1987; 7:138–48.
17. Parker SL, Guerra Valero YC, Roberts DM, Lipman J, Roberts JA, Wallis SC. Determination of cefalothin and cefazolin in human plasma, urine and peritoneal dialysate by UHPLC-MS/MS: application to a pilot pharmacokinetic study in humans. *Biomed Chromatogr* 2015; Sep 23. [Epub ahead of print].
18. Bergeron MG, Brusch JL, Barza M, Weinstein L. Bactericidal activity and pharmacology of cefazolin. *Antimicrob Agents Chemother* 1973; 4:396–401.
19. Rein MF, Westervelt FB, Sande MA. Pharmacodynamics of cefazolin in the presence of normal and impaired renal function. *Antimicrob Agents Chemother* 1973; 4:366–71.
20. Craig WA, Andes DR. *In vivo* pharmacodynamics of ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. *Antimicrob Agents Chemother* 2008; 52:3492–6.
21. Tosukhowong T, Eiam-Ong S, Thamutok K, Wittayalertpanya S, Na Ayudhya DP. Pharmacokinetics of intraperitoneal cefazolin and gentamicin in empiric therapy of peritonitis in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 2001; 21:587–94.
22. Yamasaki F, Tsuchida R, Usuda Y. A study of the kinetics of cephalosporins in renal impairment. *Postgrad Med J* 1970; (Suppl):57–9.
23. Moellering RC, Jr, Swartz MN. Drug therapy: the newer cephalosporins. *N Engl J Med* 1976; 294:24–8.
24. Szeto CC, Chow KM, Kwan BC, Law MC, Chung KY, Yu S, *et al.* *Staphylococcus aureus* peritonitis complicates peritoneal dialysis: review of 245 consecutive cases. *Clin J Am Soc Nephrol* 2007; 2:245–51.
25. Barretti P, Doles JV, Pinotti DG, El Dib R. Efficacy of antibiotic therapy for peritoneal dialysis-associated peritonitis: a proportional meta-analysis. *BMC Infect Dis* 2014; 14:445.
26. Govindarajulu S, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, *et al.* *Staphylococcus aureus* peritonitis in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in 503 cases. *Perit Dial Int* 2010; 30:311–9.
27. Burke M, Hawley CM, Badve SV, McDonald SP, Brown FG, Boudville N, *et al.* Relapsing and recurrent peritoneal dialysis-associated peritonitis: a multicenter registry study. *Am J Kidney Dis* 2011; 58:429–36.