Administration of Tobramycin in the Beginning of the Hemodialysis Session: A Novel Intradialytic Dosing Regimen

Osama Hussein Kamel Mohamed,* Ihab M. Wahba,† Suzanne Watnick,†‡ Sandra B. Earle,§ William M. Bennett,‖** James W. Ayres,¶ and Myrna Y. Munar**

**Faculty of Pharmacy, Pharmaceutics Department, Cairo University, Cairo, Egypt; †Division of Nephrology and Hypertension, Department of Medicine, Oregon Health & Science University, Portland, Oregon; ‡Division of Hospital and Specialty Medicine, Portland Veterans Administration Medical Center, Portland, Oregon; §Department of Pharmacy Practice, Findlay University School of Pharmacy, Findlay, Ohio; ‖Solid Organ and Cellular Transplantation, Legacy Good Samaritan Hospital, Portland, Oregon; **Department of Pharmacy Practice, Oregon State University College of Pharmacy, Portland Campus at Oregon Health & Science University, Portland, Oregon; and ¶Department of Pharmaceutical Sciences, Oregon State University College of Pharmacy, Corvallis, Oregon*

Background: Aminoglycoside antibiotic efficacy is related to peak concentration (C_{max}) and postantibiotic effect, whereas toxicity is directly related to body exposure as measured by area under the serum concentration *versus* time curve (AUC). On the basis of pharmacokinetic simulation models, tobramycin administration during the first 30 min of high-flux hemodialysis achieves similar C_{max} but significantly lower AUC and prehemodialysis concentrations compared with conventional dosing in the last 30 min of hemodialysis.

Design, setting, participants, and measurements: To test this hypothesis, a pilot study in which five adult chronic hemodialysis patients who were undergoing high-flux dialysis received one dose of tobramycin 1.5 mg/kg intravenously during the first or last 30 min of hemodialysis was conducted. After a 1-mo washout period, patients crossed over to the other treatment schedule. Tobramycin serum concentrations were measured to determine C_{max}, interdialytic and intradialytic elimination rate constants and half-lives, AUC, and clearance.

Results: Tobramycin administration during the first and last 30 min of hemodialysis resulted in similar C_{max} of 5.63 ± 0.49 and 5.83 ± 0.67 mg/L ($P > 0.05$) but significantly lower prehemodialysis concentrations of 0.16 ± 0.09 and 2.44 ± 0.43 mg/L ($P < 0.001$) and AUC of 21.06 and 179.23 ± 25.84 mg/h per L ($P < 0.001$), respectively.

Conclusions: Tobramycin administration during the first 30 min of hemodialysis results in similar C_{max} but lower AUC to conventional dosing, which may translate into comparable efficacy but lower toxicity.

Clin J Am Soc Nephrol 2: 694-699, 2007. doi: 10.2215/CJN.01600407

Aminoglycoside antibiotics are bactericidal drugs that are used for empiric and active treatment of Gram-negative infections. Despite their proven effectiveness, the use of aminoglycosides in hemodialysis patients is limited by ototoxicity and vestibular toxicity, which could be as high as 30% (1). Aminoglycoside efficacy is related to peak concentration (C_{max}) and the postantibiotic effect (2), namely a period of suppression of bacterial regrowth after brief exposure to the antibiotic. In contrast, aminoglycoside toxicity is directly related to body exposure as measured by the area under the serum concentration *versus* time curve (AUC) (3). Because aminoglycosides are mainly administered for synergy with other antibiotics, high predialysis levels may not be necessary for efficacy. A recommended dosing regimen for aminoglycosides in adult hemodialysis patients is to administer half of the dose that is given to a patient with normal renal function after each hemodialysis session or during the last 30 to 60 min of hemodialysis (4). With this dosing regimen, a relatively high AUC and elevated prehemodialysis concentrations may ensue, resulting in an increased potential for toxicity (3,5).

We tested a new dosing schedule that takes advantage of same-session hemodialysis for drug clearance to decrease the risk for aminoglycoside toxicity. The study dosing method changes the time of aminoglycoside administration to the first instead of the last 30 min of the hemodialysis session. On the basis of several one-compartment infusion model simulations, we hypothesized that dosing aminoglycosides in the first 30 min of hemodialysis would achieve similar C_{max} but significantly lower prehemodialysis concentrations and AUC. The rationale for this dosing regimen was to minimize toxicity by reducing AUC and the duration of drug exposure while maintaining efficacy by providing adequate C_{max} and postantibiotic effect.

Received April 6, 2007. Accepted April 30, 2007.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Myrna Y. Munar, Department of Pharmacy, Oregon State University College of Pharmacy, Portland Campus at Oregon Health & Science University, 3303 SW Bond Avenue, Mail Code CH12C, Portland, OR 97239. Phone: 503-494-5164; Fax: 503-494-8797; E-mail: munarm@ohsu.edu

ISSN: 1555-9041/204–0694

The study objective was to compare C_{max}, prehemodialysis serum concentrations, and AUC after tobramycin administration in the first 30 min of hemodialysis (study method) *versus* standard dosing in the last 30 min of hemodialysis (conventional method). A secondary objective was to validate the precision and accuracy of the associated pharmacokinetic (PK) simulations in predicting tobramycin concentrations in hemodialysis patients.

Materials and Methods

Study Design

This was a prospective, crossover PK pilot study. The study was approved by the Portland Veterans Administration Medical Center (PVAMC) institutional review board.

PK Simulation Model

Computer spreadsheet programs were used to construct PK simulation models that incorporate published PK parameters such as volume of distribution and inter- and intradialytic elimination rate constants and clearance to predict drug concentrations that arise from various dosing regimens (6,7). A unique advantage to this approach is that dialyzer-specific PK parameters can be easily incorporated into the model.

A one-compartment intravenous infusion model with first-order elimination was used to construct the tobramycin PK simulation (Microsoft Office Excel 2003; Microsoft Corp, Redmond, WA). Patient-specific information (weight, tobramycin dosage, and dose timing) and population PK information (volume of distribution and interdialytic and intradialytic elimination rate constants for the Gambro PF210H dialyzer, Gambro Renal Products, Lakewood, CO) were used to construct each simulation. The tobramycin PK simulation model was used to determine the most appropriate dosing scheme for hemodialysis patients in this study. The PK simulation model was validated prospectively using measured serum tobramycin concentrations.

Study Population

From a pool of 25 potential patients, five adult, noninfected, male, chronic hemodialysis patients participated in this study after providing verbal and written informed consent. All five patients had negligible residual renal function (RRF; urine output <250 ml/d). Exclusion criteria were a history of hypersensitivity to aminoglycosides, morbid obesity (weight >50% of ideal body weight), concomitant use of other ototoxic agents, history of significant ototoxicity or vestibular dysfunction, and severe hepatic disease.

Study Procedure

Patients received a single dose of tobramycin 1.5 mg/kg total body weight intravenously during the first 30 min (study method) or the last 30 min (conventional method) of hemodialysis. After a 1-mo washout period, patients were crossed over to receive the other treatment schedule. Tobramycin sulfate was dissolved in 250 ml of normal saline and administered by an infusion pump over 30 min. The standard duration of dialysis in these study patients was not changed and ranged from 4.0 to 4.5 h. All patients used the Gambro PF210H dialyzer (synthetic, 2.1 M^2, KUf 85) for both study phases. Blood flow rate and dialysate flow rate were kept constant at 400 and 600 ml/min, respectively. Patient medications and blood chemistries were reviewed to avoid drug or disease interactions during the study. Low- and high-frequency hearing tests were performed at the PVAMC Audiology Clinic before and within 3 d after tobramycin administration.

Figure 1 illustrates the blood sampling scheme for each dosing method. When patients received 1.5 mg/kg tobramycin intravenously during the first 30 min of hemodialysis, four blood samples were collected from the patient through the arterial line of the dialysis circuit. Samples were taken before the start of dialysis (control), 1 h after the end of drug infusion (postinfusion), at the end of dialysis, and just before the next dialysis session (prehemodialysis). When patients received tobramycin 1.5 mg/kg tobramycin intravenously during the last 30 min of hemodialysis, three blood samples were collected from the patient through the arterial line. Samples were obtained before the start of drug infusion (control), 1 h after the end of drug infusion (postinfusion), and just before the next dialysis session (prehemodialysis).

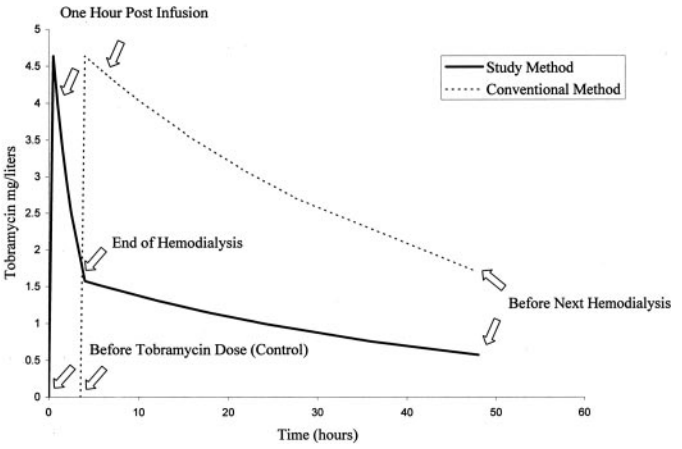

Figure 1. Blood sampling scheme.

Two milliliters of blood was collected in BD Vacutainer SST gel and clot activator tubes (BD, Franklin Lakes, NJ). Samples were sent to the PVAMC central laboratory immediately after collection and analyzed for serum tobramycin concentration using a validated fluorescence polarization immunoassay (TDx; Abbott Laboratories, Irving, TX). The lower limit of detection was 0.1 mg/L.

PK Analysis

Measured postinfusion serum tobramycin concentrations were back-extrapolated to determine the maximum drug concentrations at the end of the infusion (C_{max}) for both dosing schedules. Measured tobramycin concentrations during dialysis and between the dialysis sessions were used to calculate intradialytic and interdialytic elimination rate constants, respectively. Intradialytic and interdialytic half-lives were calculated as a function of the elimination rate constants using the expression 0.693/k. AUC was determined using the trapezoidal rule and extrapolated to infinity ($AUC_{0-\infty}$). Clearance was calculated as dose/$AUC_{0-\infty}$.

Statistical Analyses

Descriptive statistics were used to describe patient demographics. ANOVA was used to determine statistically significant differences in C_{max}, prehemodialysis concentrations, and AUC between the two dosing schedules (S-Plus 2000; Mathsoft Engineering & Education, Cambridge, MA). $P < 0.05$ was considered to be statistically significant. The predictive performance of the tobramycin PK simulation model was also determined (8). The mean prediction error and the root mean squared prediction error were calculated as measures of bias and precision, respectively.

Results

Patient Demographics

Five adult male chronic, stable hemodialysis patients participated in the study. Patient demographics are summarized in Table 1.

Table 1. Patient demographics

Patient	Age (yr)	Gender	Race	Weight (kg)	Years on Dialysis	Cause of ESRD
1	53	M	White	101	1.5	Diabetes
2	70	M	White	110	1.0	Diabetes
3	57	M	White	90.5	4.5	Unknown
4	54	M	Black	81	5.5	Hypertension
5	61	M	Black	114	1.0	Diabetes
Mean ± SD	59 ± 6.89			99.3 ± 13.65	2.7 ± 2.14	

PK Analysis

Measured serum tobramycin concentrations that were obtained from each study patient are shown in Table 2. Table 3 summarizes calculated C_{max}, prehemodialysis concentrations, and AUC for both dosing regimens. Tobramycin PK parameters are shown in Table 4.

The results show that there is no statistically significant difference between the study and the conventional dosing regimens in C_{max} (5.63 ± 0.49 and 5.83 ± 0.67 mg/L, respectively; $P = 0.243$), whereas there is a statistically significant difference between both dosing regimens in drug prehemodialysis concentrations and AUC. The study dosing regimen resulted in lower postdialysis concentrations (0.38 ± 0.16 mg/L) that remained low until the next hemodialysis session (prehemodialysis concentration 0.2 ± 0.1 mg/L). Prehemodialysis concentrations reached the lower limit of tobramycin assay sensitivity in three of five patients. Four of five patients who received tobramycin during the last 30 min of dialysis had prehemodialysis concentrations >2 mg/L. The study method also yielded smaller AUC than the conventional dosing regimen (study method 21.06 ± 6.24 mg × h/L; conventional method 179.23 ± 25.84 mg × h/L; $P < 0.001$ for both parameters).

Figure 2 shows the best fit lines for simulated serum concentration *versus* time data for both the study and conventional methods. In the study method, C_{max} occurred 30 min after that start of the dialysis session. Drug concentrations then rapidly declined until the end of hemodialysis. Intradialytic half-life was less than 1 h with an average intradialytic clearance of 5.46 ± 1.53 L/h. From the end of dialysis until the time of the next dialysis session, drug cleared very slowly as a result of negligible RRF. In the conventional dosing regimen, C_{max} occurred at the end of hemodialysis. Interdialytic half-life was prolonged at an average of 35.92 ± 6.11 h with a reduced interdialytic clearance of 0.50 ± 0.14 L/h. As a result, posthemodialysis concentrations were relatively high for >40 h (Figure 2), and prehemodialysis concentrations were >2 mg/L in four of five patients. In addition, the AUC for the conventional method was almost 8.5 times greater than that of the study method ($P < 0.001$).

Figure 3 shows performance of the tobramycin PK simulation in predicting measured tobramycin concentrations in hemodialysis patients. The tobramycin PK simulation model predicted measured tobramycin concentrations with good accuracy and precision. The majority of tobramycin drug concentrations centered around the line of identity. The simulation model slightly underpredicted measured tobramycin concentrations with negative bias observed for C_{max}, 1 h after infusion, end of hemodialysis, and prehemodialysis concentrations.

Adverse Effects

Hearing tests for each patient showed no difference in hearing acuity before and after drug administration. There was no clinically evident vestibular dysfunction after drug administration in any of the patients.

Table 2. Tobramycin dose administered and the resultant serum tobramycin concentrations[a]

Patient	Dosage (mg; 1.5 mg/kg)	Measured Serum Tobramycin Concentrations (mg/L)						
		Conventional Method			Study Method			
		Before Drug Infusion (Control)	1 h after Infusion	Before Next HD	Before Start of HD (Control)	1 h after Infusion	End of HD	Before Next HD
1	150	0	6.1	2.6	0	2.5	0.3	0.1
2	160	0	5.1	1.7	0	2.3	0.3	0.1
3	140	0	5.7	2.6	0	3.1	0.6	0.3
4	120	0	6.6	2.8	0	2.3	0.2	0.1
5	165	0	5.1	2.5	0	2.6	0.5	0.2
Average ± SD	147 ± 17.89	0	5.83 ± 0.67	2.44 ± 0.43	0	2.56 ± 0.33	0.38 ± 0.16	0.2 ± 0.1

[a]HD, hemodialysis.

Table 3. C_{max} and pre-HD tobramycin serum concentration and AUC for the conventional and study dosing methods[a]

Patient	C_{max} (mg/L)		Pre-HD (mg/L)[b]		AUC (mg × h/L)[b]	
	Study Method	Conventional Method	Study Method	Conventional Method	Study Method	Conventional Method
1	5.85	6.23	0.1	2.6	17.94	194.77
2	5.2	5.18	0.1	1.7	17.1	152.64
3	5.98	5.8	0.3	2.6	30.46	185.65
4	6.11	6.73	0.1	2.8	15.46	210.45
5	5.03	5.2	0.2	2.5	24.35	152.65
Average ± SD	5.63 ± 0.49	5.83 ± 0.67	0.16 ± 0.09	2.44 ± 0.43	21.06 ± 6.24	179.23 ± 25.84

[a]AUC, area under the serum concentration *versus* time curve; C_{max}, maximum concentration.
[b]$P < 0.001$ study method *versus* conventional method.

Table 4. Tobramycin pharmacokinetic parameters[a]

Patient	K_{HD} (/h)	K_{NHD} (/h)	$t_{1/2}$HD (h)	$t_{1/2}$NHD (h)	$AUC_{0-\infty}$ (mg × h/L)		CL (L/h)	
					Study Method	Conventional Method	Study Method	Conventional Method
1	0.85	0.019	0.82	36.47	23.20	331.61	6.46	0.45
2	0.82	0.016	0.85	43.31	23.35	258.89	6.85	0.62
3	0.66	0.018	1.05	38.50	47.13	330.09	2.97	0.42
4	0.98	0.020	0.71	34.65	20.46	350.45	5.87	0.34
5	0.66	0.026	1.05	26.65	32.04	248.80	5.15	0.66
Average ± SD	0.79 ± 0.14	0.020 ± 0.004	0.90 ± 0.15	35.92 ± 6.11	29.24 ± 10.91	303.97 ± 46.59	5.46 ± 1.53	0.50 ± 0.14

[a]$AUC_{0-\infty}$, area under the serum concentration versus time curve from 0 to ∞; CL, clearance; K_{HD}, elimination rate constant during hemodialysis; K_{NHD}, elimination rate constant between hemodialysis sessions; $t_{1/2}$HD, elimination half-life during hemodialysis; $t_{1/2}$NHD, elimination half-life between hemodialysis sessions.

Discussion

This is the first pilot study performed in noninfected hemodialysis patients to investigate the PK of a novel intradialytic dosing regimen of tobramycin in the beginning of dialysis. Tobramycin administration during the first and last 30 min of dialysis resulted in comparable drug peaks but significantly less drug exposure as observed by significantly reduced AUC by 90% and prehemodialysis concentrations to <2 mg/L in all patients. Because tobramycin efficacy is directly related to its peak concentration and the postantibiotic effect, whereas toxicity is related to AUC, the proposed study regimen has the potential to reduce toxicity while maintaining efficacy (2,3).

Aminoglycoside ototoxicity is often debilitating and is well documented in both hemodialysis and peritoneal dialysis patients (5,9). In a series of 21 hemodialysis patients who received gentamicin dosages of 1 to 1.5 mg/kg thrice weekly after dialysis, the incidence of ototoxicity was 30% and was mostly vestibular. Patient age, duration of drug exposure, and total dosage were significantly higher in patients who developed ototoxicity compared with control subjects. C_{max} was not statistically different between the two groups (5). Thus, diminished total drug exposure as in the proposed study method dosing regimen could lessen drug toxicity in hemodialysis.

Aminoglycoside nephrotoxicity is also well documented (10) and may cause loss of RRF in patients who undergo dialysis. Dialysis patients with any RRF have been shown to have a better survival than those with less function. This is well documented in peritoneal dialysis, where a residual GFR of 5 to 10 L/wk confers a 12% reduction in mortality, and an increase in urine output by 250 ml/d is associated with a 34% risk for death reduction irrespective of peritoneal clearances (11,12). RRF, even at a low level, was also associated with a lower risk for mortality in hemodialysis patients (13). More recently, investigators from Europe found that there was a 56% reduction in the risk for death in hemodialysis patients with each 1-U increase in weekly residual renal Kt/V_{urea} (14). A lower total exposure to aminoglycosides in hemodialysis patients therefore is desirable to preserve RRF, which could have an impact on patient survival.

PK computer simulations are valuable tools that allow prediction of drug concentrations that result from various dosing regimen iterations. The tobramycin PK simulations that were performed in this study predicted measured concentrations with excellent accuracy and precision. The PK simulation model can thus be used to determine optimal tobramycin dosages that safely achieve greater concentration-dependent bac-

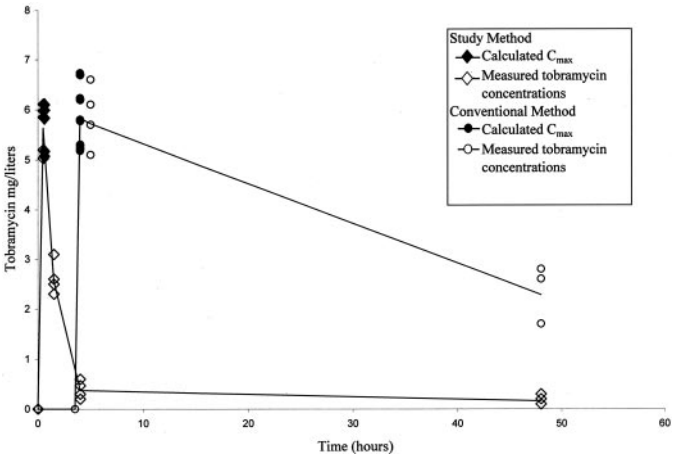

Figure 2. Pharmacokinetic simulations and measured serum tobramycin concentrations ($n = 5$). Time zero on the *x*-axis is the start time of the dialysis session. The lines are the simulations and the data points are the calculated C_{max} and the measured serum concentrations (1 hour postinfusion, end of hemodialysis, and before next hemodialysis concentrations) for all patients.

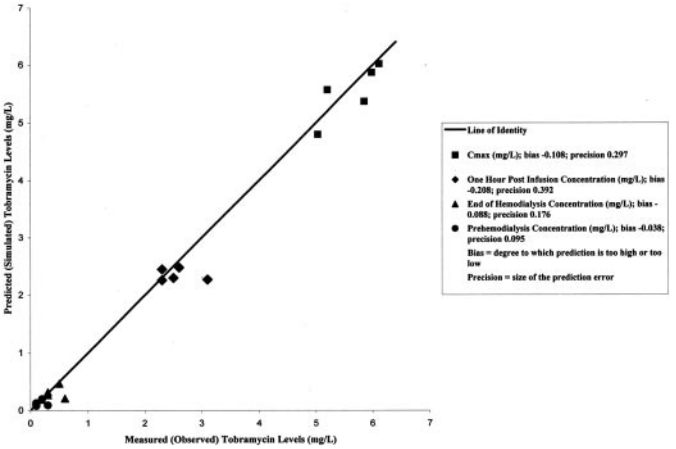

Figure 3. Predictive performance of tobramycin PK simulation model in hemodialysis patients.

tericidal activity in infected hemodialysis patients. Using a simulation model, Teigen *et al.* (15) suggested that higher dosages of gentamicin, given immediately before dialysis at 300 mg as the first dose, 240 mg as the second dose, and 220 mg as the third dose, had a higher probability of achieving C_{max} >8 mg/L and acceptable exposure limits (AUC values >70 and <120 mg/h per L) in patients who were undergoing hemodialysis three times a week. Dang and Duffull (16) used a simulation model to test various predialysis dosages of gentamicin and found that an initial dosage of 230 to 240 mg administered within 2 h before dialysis could achieve a better PK profile than postdialysis dosing. Although these simulation models were not tested *in vivo*, they are likely to be highly accurate, similar to our model.

This study has many limitations, such as the small sample size. Because this is a pilot study conducted in noninfected dialysis patients, it was difficult to justify a larger study with a potentially toxic agent. Furthermore, the sample size had sufficient power to support the conclusions. Certainly, the results could help design larger studies in infected patients. Another limitation of our study is our inability to verify the efficacy of the proposed tobramycin dosing regimen because the study was conducted in noninfected patients and because the AUC with the proposed method may be too small. The determinants of aminoglycoside efficacy include the C_{max}:minimum inhibitory concentration (MIC) ratio and the AUC:MIC ratio (17–20). In a recent pharmacodynamic study of treatment and outcome in 38 cases of *Pseudomonas aeruginosa* bacteremia, the C_{max}:MIC ratio and not the AUC:MIC ratio was found to be independently associated with treatment outcome in multivariable logistic regression analysis (20). In this study, the median C_{max}:MIC ratio was 5.3 (interquartile range 4.5 to 9.5) for patients who achieved clinical cure and 3.2 (interquartile range 2.1 to 4.6) for patients with clinical failure. In our study, the proposed and conventional tobramycin dosing resulted in similar C_{max} of 5.63 ± 0.49 and 5.83 ± 0.67 mg/L respectively. This translated to a C_{max}:MIC ratio of approximately 5.7 for *Escherichia coli* and 2.85 for *Pseudomonas aeruginosa* for both methods. The C_{max}:MIC ratio of both methods in our study therefore may not be adequate for the treatment of pseudomonal infections. Higher intradialytic or predialytic dosing of tobramycin may provide higher concentration and more effective killing. Previous simulation studies of predialysis dosing support this hypothesis but need prospective confirmation in the clinical setting (15,16).

Because aminoglycosides are seldom administered alone for treatment of Gram-negative infections and are usually administered in combination with β-lactam or other cell wall–active antibiotics to confer synergistic bactericidal activity, high and sustained levels of aminoglycosides are rarely needed in dialysis patients. In support of this concept, a group of Japanese investigators administered 2 mg/kg arbekacin intravenously just before each hemodialysis session for 2 wk and concluded that bacterial eradication was successful in most patients in this series (21). This suggests that the proposed dosing regimen in our study is likely to be clinically effective.

Conclusion

Tobramycin administration in the beginning of the hemodialysis session achieves a similar C_{max} but a lower AUC than conventional dosing in the last 30 min of dialysis. This novel dosing regimen could potentially translate into similar efficacy but lower toxicity. Further studies aimed at testing multiple and possibly higher dosing regimens in the beginning of dialysis to achieve clinical cure are needed to validate the results of this pilot study.

Acknowledgments

We acknowledge Angie Mettie for assistance in preparing this manuscript.

Disclosures

None.

References

1. Brummett RE, Morrison RB: The incidence of aminoglycoside antibiotic-induced hearing loss. *Arch Otolaryngol Head Neck Surg* 116: 406–410, 1990
2. Lacy MK, Nicolau DP, Nightingale CH, Quintiliani R: The pharmacodynamics of aminoglycosides. *Clin Infect Dis* 27: 23–27, 1998
3. Rybak MJ, Abate BJ, Kang SL, Ruffing MJ, Lerner SA, Drusano GL: Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. *Antimicrob Agents Chemother* 43: 1549–1555, 1999
4. Aronoff GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, Swan K, Bennett WM: *Drug Prescribing in Renal Failure: Dosing Guidelines in Adults*, 4th Ed., Philadelphia, American College of Physicians, 1999
5. Gailiunas P Jr, Dominguez-Moreno M, Lazarus M, Lowrie EG, Gottlieb MN, Merrill JP: Vestibular toxicity of gentamicin. Incidence in patients receiving long-term hemodialysis therapy. *Arch Intern Med* 138: 1621–1624, 1978
6. Kisor DF, Watling SM, Zarowitz BJ, Jelliffe RW: Population pharmacokinetics of gentamicin. Use of the nonparametric expectation maximisation (NPEM) algorithm. *Clin Pharmacokinet* 23: 62–68, 1992
7. Matzke GR, Halstenson CE, Keane WF: Hemodialysis elimination rates and clearance of gentamicin and tobramycin. *Antimicrob Agents Chemother* 25: 128–130, 1984
8. Sheiner LB, Beal SL: Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm* 9: 503–512, 1981
9. Chong TK, Piraino B, Bernardini J: Vestibular toxicity due to gentamicin in peritoneal dialysis patients. *Perit Dial Int* 11: 152–155, 1991
10. Paterson DL, Robson JM, Wagener MM: Risk factors for toxicity in elderly patients given aminoglycosides once daily. *J Gen Intern Med* 13: 735–739, 1998
11. Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang SM, Zhu X, Lazarus JM: Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. *Am J Kidney Dis* 33: 523–534, 1999
12. Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: A reanalysis of the CANUSA study. *J Am Soc Nephrol* 12: 2158–2162, 2001
13. Shemin D, Bostom AG, Laliberty P, Dworkin LD: Residual renal function and mortality risk in hemodialysis patients. *Am J Kidney Dis* 38: 85–90, 2001
14. Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT; NECOSAD Study Group: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 15: 1061–1070, 2004
15. Teigen MM, Duffull S, Dang L, Johnson DW: Dosing of gentamicin in patients with end-stage renal disease receiving hemodialysis. *J Clin Pharmacol* 46: 1259–1267, 2006
16. Dang L, Duffull S: Development of a semimechanistic model to describe the pharmacokinetics of gentamicin in patients receiving hemodialysis. *J Clin Pharmacol* 46: 662–673, 2006
17. Moore RD, Lietman PS, Smith CR: Clinical response to aminoglycoside therapy: Importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis* 155: 93–99, 1987
18. Vogelman B, Gudmundsson S, Turnidge J, Leggett J, Craig WA: In vivo postantibiotic effect in a thigh infection in neutropenic mice. *J Infect Dis* 157: 287–298, 1988
19. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr: Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob Agents Chemother* 43: 623–629, 1999
20. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE: Treatment and outcome of *Pseudomonas aeruginosa* bacteraemia: An antibiotic pharmacodynamic analysis. *J Antimicrob Chemother* 52: 668–674, 2003
21. Matsuo H, Hayashi J, Ono K, Andoh K, Andoh Y, Sano Y, Saruki K, Tanaka J, Yamashita M, Nakamura K, Kubo K: Administration of aminoglycosides to hemodialysis patients immediately before dialysis: A new dosing modality. *Antimicrob Agents Chemother* 41: 2597–2601, 1997