Kidney International, Vol. 63 (2003), pp. 1072–1078

Gentamicin pharmacokinetics during slow daily home hemodialysis

HAROLD J. MANLEY, GEORGE R. BAILIE, MARCY L. MCCLARAN, and WALTER L. BENDER

University of Missouri–Kansas City, Kansas City; Albany College of Pharmacy, Albany; Albany Medical College, Albany, New York; Dialysis Clinic, Inc. of Kansas City, Kansas City; and Kidney Associates of Kansas City, Kansas City, Missouri

Gentamicin pharmacokinetics during slow daily home hemodialysis.

Background. Gentamicin is commonly used in hemodialysis patients. Gentamicin pharmacokinetics during traditional hemodialysis have been described. Slow daily home (SDH) hemodialysis (7 to 9 hours a day/6 days a week) use is increasing due to benefits observed with increased hemodialysis. We determined gentamicin pharmacokinetics for SDH hemodialysis patients.

Methods. Eight patients (four male and four female) received a single intravenous dose of 0.6 mg/kg gentamicin post-hemodialysis. Blood samples were collected at 5, 10, 15, 30, and 60 minutes after dose. The next day patients underwent a typical SDH hemodialysis (high-flux F50NR dialyzer) session. Blood samples were taken at 0, 5, 15, 60, 120, 240, 360, 480 minutes during and 15, 30 and 60 minutes post-hemodialysis. Baseline and 24-hour urine samples were collected. Pharmacokinetic parameters were calculated assuming a one-compartment model.

Results. Patients were 42.5 ± 13.1 years old (mean ± SD). Inter-, intra-, and post-hemodialysis collection periods were 17.0 ± 2.1 hours, 8.1 ± 0.4 hours, and 1.1 ± 0.1 hours, respectively. Intra-, and interdialytic gentamicin half-lives were different (intradialytic, 3.7 ± 0.8 hours; interdialytic, 20.4 ± 4.7 hours; $P < 0.0001$). Hemodialysis clearance accounted for 70.5% gentamicin total clearance. Renal clearance correlated with glomerular filtration rate (GFR) (renal clearance = 1.2 GFR; $r^2 = 0.98$; $P < 0.001$). Mean peak and trough of hemodialysis concentrations were 1.8 ± 0.6 μg/mL and 0.5 ± 0.2 μg/mL, respectively. Post-hemodialysis rebound was 3.1 ± 8.8% at 1 hour.

Conclusion. Pharmacokinetic model predicts 2.0 to 2.5 mg/kg dose gentamicin post-hemodialysis would provide peak (1 hour post-dose) and trough (end of SDH hemodialysis session) concentrations of 6.0 to 7.5 μg/mL and 0.7 to 0.8 μg/mL, respectively. This would provide adequate coverage for most gram-negative organisms in SDH hemodialysis patients.

Infection remains a leading cause of morbidity and mortality in end-stage renal disease (ESRD) patients [1, 2]. These patients are at an increased risk of infection due to defects in cellular immunity, neutrophil function, and complement activation [3, 4]. Therefore, antibiotics are often used empirically in an outpatient dialysis setting.

Gentamicin, an aminoglycoside antibiotic, may be used empirically due to its efficacy against many gram-negative organisms. Gentamicin pharmacokinetics during traditional three times a week hemodialysis has been characterized [5–12]; however, the information provided is limited or rendered obsolete, at least in part due to advances in dialysis technology over the past 20 years. One such advancement is slow daily home (SDH) hemodialysis, in which patients are dialyzed 6 nights a week for 7 to 9 hours each night. This treatment has been advocated because it has been demonstrated that increased frequency and longer duration of treatment results in improved patient outcomes [13–17].

As gentamicin is frequently used in dialysis patients, issues regarding its pharmacokinetics in SDH hemodialysis patients are pertinent. Gentamicin serum concentrations are routinely monitored to assure maximal efficacy and safety due to its relatively narrow therapeutic index. Gentamicin pharmacokinetics determined during three times a week, 3 to 4 hour sessions, should not be extrapolated to SDH hemodialysis patients. No published studies exist that specifically address gentamicin dosing in these patients. We characterized gentamicin pharmacokinetic parameters during a typical SDH hemodialysis session and from these developed dosing recommendations.

METHODS

This study was conducted at an outpatient dialysis unit (Dialysis Clinic, Inc., Kansas City, MO, USA) as a prospective, open-label, gentamicin pharmacokinetic study in ESRD hemodialysis patients. Adult (18 years old or older), noninfected, chronic hemodialysis patients were eligible for participation. Both patients with and without residual renal function were studied. Nonanuric patients concurrently receiving medications with the potential to inhibit active tubular secretion (e.g., H_2-antagonists)

Key words: gentamicin, pharmacokinetics, slow daily home hemodialysis, dosing.

Received for publication January 2, 2002
and in revised form July 19, 2002, and August 28, 2002
Accepted for publication October 16, 2002

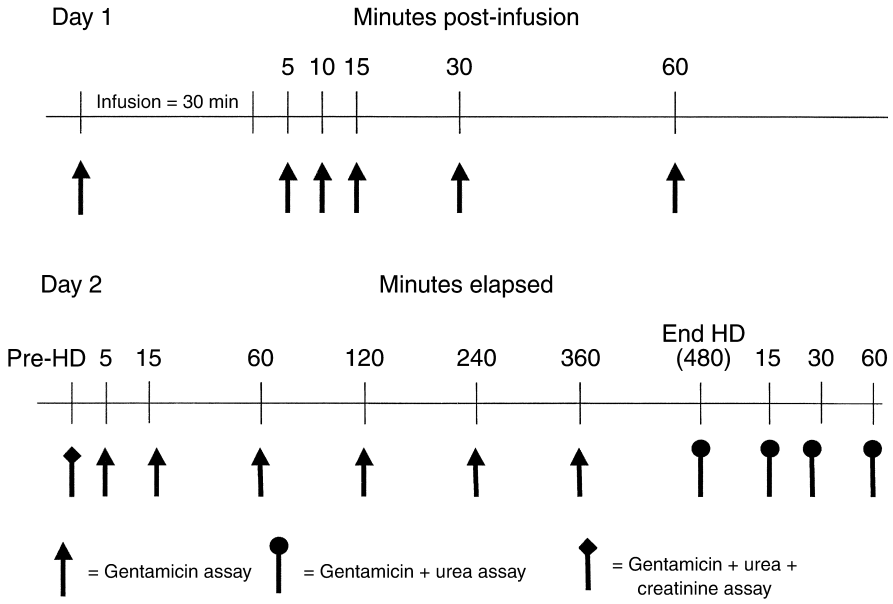

Fig. 1. Study design.

were allowed to enter the study after a 2-week washout period. Patients could not receive any aminoglycoside antibiotics within 2 weeks prior to their participation. Patients with stated or documented allergies to aminoglycosides were not eligible. Participation of each volunteer lasted approximately 48 hours. The protocol was approved by the Adult Health Sciences Review Board of the University of Missouri-Kansas City and Dialysis Clinic, Inc. All subjects gave written informed consent before participation.

Dialysis prescription

All subjects had a standardized 8-hour hemodialysis session typical of SDH hemodialysis. Blood flow rate and dialysate flow rates were 200 mL/minute and 300 mL/minute, respectively. All patients used a high-flux polysulfone F50 dialysis filter (Fresenius Medical Care, Lexington, MA, USA) that has a surface area of 0.5 m^2. All patients used central double-lumen venous catheters for dialysis access.

Gentamicin administration

Subjects received 0.6 mg/kg actual body weight (rounded to nearest 10 mg) of gentamicin (Schein, Florham Park, NJ, USA) immediately upon completion of a hemodialysis session, after weight (kg) and height (cm) were recorded. The gentamicin was prepared according to the manufacturer's recommendations and was administered through the in-dwelling venous hemodialysis catheter over approximately 30 minutes. The venous catheter was then flushed with 10 mL saline to ensure that the entire gentamicin dose was given to the patient. After the saline flush, the venous catheter was utilized for the duration of that study for venous sampling.

Blood sampling

Five milliliters of venous blood was collected in standard blood collection tubes containing no anticoagulant (serum separator tubes) at baseline (prior to gentamicin dose) and at the following times after completion of dose administration: 5, 10, 15, 30, and 60 minutes post-gentamicin administration. (Fig. 1)

At the next scheduled hemodialysis session, post-voiding pre-dialysis and post-dialysis weights were recorded. Seven milliliters of blood were collected (red-top tubes) pre-dialysis, at the end of hemodialysis, and 15, 30, and 60 minutes after dialysis for determination of urea and gentamicin concentration. Five milliliters of blood were collected (red-top tubes) at 5, 15, 60, 120, 240, and 360 minutes into the hemodialysis treatment for gentamicin concentration determination. (Fig. 1) All blood samples were obtained from the arterial line.

Urine collection

Nonanuric subjects spontaneously voided immediately after the first hemodialysis. An aliquot (10 mL) was saved and tested to ensure no interfering substances were present which would invalidate the assay used for gentamicin determination in urine. All urine produced up until the end of the next scheduled dialysis treatment was collected, measured, and an aliquot (10 mL) frozen at −70°C until the time of assay.

Sample preparation and analysis

After being allowed to clot for at least 30 minutes, sera was collected and then frozen to at least −70°C until analysis. The urine and serum concentrations of gentamicin were determined by fluorescence polariza-

Table 1. Patient demographics

Patient	Gender	Age *years*	ESRD diagnosis	ABW *kg*	Height *cm*	BSA m^2	Urine *mL/24 hours*	24-hour GFR *mL/min/1.73* m^2	Gentamicin dose *mg*
A	M	40.5	Alport syndrome	73.0	182.9	1.93	0	0	40
B	F	33.8	GN	54.7	152.4	1.52	30	0.05	30
C	M	45.8	DM	113.1	162.6	2.26	10	0.08	70
D	M	68.3	Obstructive uropathy	79.1	188.0	2.03	1350	5.90	50
E	M	31.0	GN	153.0	175.3	2.73	100	0.57	90
F	F	48.7	HTN	70.4	165.1	1.80	100	0.54	50
G	F	46.0	HTN	96.8	167.6	2.12	30	0.30	60
H	F	26.1	GN	54.4	157.5	1.54	0	0	30
Mean		42.5		86.8	168.9	1.99	231.4	1.24	52.5
SD		13.1		33.3	12.3	0.40	494.9	2.29	20.5

Abbreviations are: ESRD, end stage renal disease; ABW, actual body weight; BSA, body surface area; GFR, glomerular filtration rate; F, female; M, male; DM, diabetes mellitus; GN, glomerulonephritis; HTN, hypertension.

tion immunoassay (TDx; Abbott Laboratories, Abbott Park, IL, USA). The lower limits of quantification for gentamicin was 0.3 μg/mL. Determination of urine urea and creatinine and serum urea and creatinine was performed using standard methodology. All assays occurred at a central laboratory (Albany Medical Center, Albany, NY, USA).

Data analysis

Gentamicin serum concentration results were modeled using PK-Analyst® (MicroMath, version 1.0, Salt Lake City, UT, USA) pharmacokinetic data analysis software. A monoexponential model was assumed and pharmacokinetic parameters were calculated using standard formulas. Other calculations performed included glomerular filtration rate (GFR) and adequacy of dialysis [urea reduction ratio (URR)] and Kt/V [18, 19]. All equations utilized are provided in the appendix.

Data are presented as mean ± SD. Nonanuric and anuric patient results were compared using Student *t* test. Pearson correlations were performed to determine an association between GFR and renal clearance and dialysis adequacy parameters (URR and Kt/V) and gentamicin hemodialysis clearance. A *P* value less than 0.05 was considered statistically significant. SigmaStat for the PC (Jandel Scientific, version 1.0, San Rafael, CA, USA) was used to perform the statistical calculations.

RESULTS

Eight patients were enrolled into the study. The mean duration on ESRD was 5.6 ± 5.4 years (range, 2 to 19 years). The patient demographics are shown in Table 1. Two patients were anuric and five more were oliguric (<400 mL urine/24 hours). The mean GFR was 1.24 ± 2.29 mL/min/1.73 m^2.

Summaries of gentamicin pharmacokinetic parameters are shown in Table 2. The mean intra- and interdialytic times were 17.0 ± 2.1 hours and 8.1 ± 0.4 hours, respectively. The inter- and intradialytic elimination half-lives were significantly different ($t_{1/2}$ inter- and intradialytic = 20.4 ± 4.7 hours; $t_{1/2}$ hemodialysis = 3.7 ± 0.8 hours; $P < 0.0001$). The mean elimination rate constants for interdialytic period (k_{ID}) and for intradialytic (k_{HD}) were 0.04 ± 0.01 $hour^{-1}$ and 0.19 ± 0.04 $hour^{-1}$, respectively. The gentamicin rebound was 3.1%, 4.4%, and 3.1% at 15, 30, and 60 minutes post-hemodialysis, respectively. The amount of gentamicin removed by the hemodialysis procedure was 70.5 ± 19.3% administered dose. Gentamicin serum concentrations over time in a typical patient (patient F) can be seen in Figure 2.

Table 2. Gentamicin volume of distribution, elimination rate constants, and corresponding half-lives on and off hemodialysis

Patient	K_{HD} h^{-1}	$t_{1/2}$ HD *h*	K_{ID} h^{-1}	$t_{1/2}$ ID *h*	Vd *L/kg*
A	0.15	4.6	0.03	26.8	0.24
B	0.23	3.0	0.03	23.6	0.25
C	0.16	4.5	0.05	15.1	0.25
D	0.20	3.5	0.06	12.3	0.29
E	0.14	4.9	0.03	22.9	0.24
F	0.26	2.6	0.03	21.6	0.36
G	0.19	3.8	0.03	21.4	0.32
H	0.23	3.0	0.04	19.8	0.31
Mean	0.19	3.7	0.04	20.4	0.28
SD	0.04	0.8	0.01	4.7	0.05

Abbreviations are: k_{el}, serum elimination rate; $t_{1/2}$, half-life; Vd, volume of distribution; HD, intradialytic; ID, interdialytic.

The mean gentamicin total clearance (during hemodialysis) was 108.2 ± 43.4 mL/min/1.73 m^2. Gentamicin hemodialysis clearance was 75.9 ± 38.4 mL/min/1.73 m^2, accounting for 70.1% of total clearance, respectively. Summaries of gentamicin clearances and patient hemodialysis adequacy are shown in Table 3. The correlation (r) between GFR and gentamicin renal clearance was 98% (renal clearance = 1.2 GFR; $P = 0.001$, beta = 0.90). The correlation between gentamicin hemodialysis clearance and URR was 0.65 (hemodialysis clearance = 163.8 URR − 22.2; $P = 0.08$, beta = 0.48). The correlation between gentamicin hemodialysis clearance and Kt/V was 0.61 (hemodialysis clearance = 59.26 Kt/V + 5.95; $P = 0.11$, beta = 0.49). No significant difference was

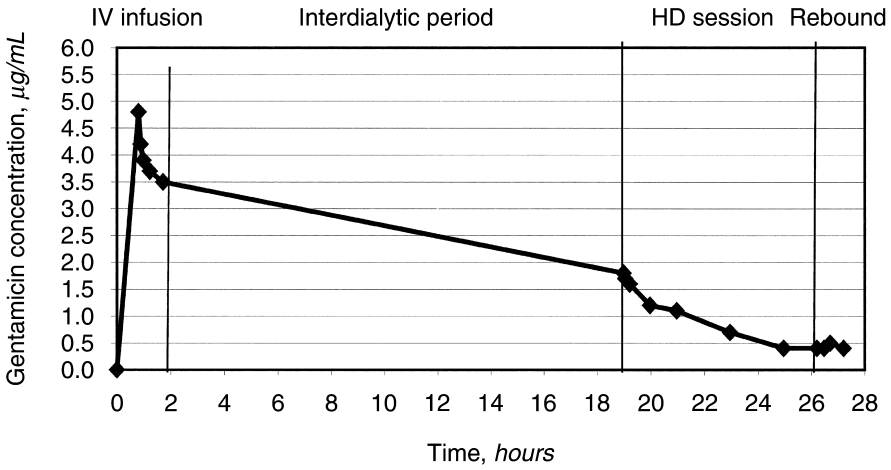

Fig. 2. Gentamicin concentration versus time profile in a representative patient F following 0.6 mg/kg infusion. Note: The x axis is not a linear scale.

Table 3. Gentamicin clearances and hemodialysis dialysis adequacy

Patient	CL_T *mL/min/1.73 m²*	CL_R *mL/min/1.73 m²*	CL_{ID} *mL/min/1.73 m²*	CL_{HD} *mL/min/1.73 m²*	CL_{IT} *mL/min/1.73 m²*	UF *L*	URR	KT/V
A	165.2		21.8	121.6	143.4	0.10	0.66	1.2
B	181.7	0.00	20.5	140.8	161.3	0.00	0.73	1.5
C	70.7	0.01	16.6	37.6	54.2	4.30	0.36	0.6
D	87.6	6.20	17.9	45.5	63.5	1.70	0.59	1.1
E	67.1	0.04	11.7	43.7	55.4	5.40	0.40	0.7
F	118.8	0.04	13.1	92.4	105.6	2.20	0.74	1.6
G	89.1	0.04	13.5	62.1	75.6	0.80	0.66	1.2
H	85.5		11.2	63.2	74.4	1.90	0.75	1.6
Mean	108.2	1.1	15.8	75.9	91.7	2.03	0.61	1.2
SD	43.4	2.5	4.0	38.4	41.0	1.96	0.15	0.4

Abbreviations are: CL_T, total body clearance; CL_R, renal clearance; CL_{ID}, interdialytic clearance; CL_{HD}, hemodialysis clearance; CL_{IT}, intradialytic clearance; UF, ultrafiltration; URR, urea reduction ratio.

Table 4. Model predicted gentamicin serum concentrations in a 70 kg individual undergoing typical slow daily home hemodialysis

	Gentamicin 2 mg/kg	Gentamicin 2.5 mg/kg
	Serum concentration *μg/mL*	
After infusion	6.0	7.5
Prior to hemodialysis	3.0	3.7
After hemodialysis	0.7	0.8
Prior to next dose	0.7	0.8

observed for any pharmacokinetic parameter between anuric and nonanuric patients.

Model predicted serum gentamicin concentrations, for a 70 kg individual post-hemodialysis administration, are shown in Table 4. Model predicted 1-hour post-infusion, pre-hemodialysis, and post-hemodialysis gentamicin serum concentrations would be adequate to maintain concentrations for sensitive organisms (serum concentrations between 7.5 μg/mL (peak 1-hour post-dose) and 0.7 μg/mL (trough end of SDH hemodialysis session). [20] For infectious processes that require higher serum concentrations (e.g., pneumonia), higher doses may be necessary. Figure 2 illustrates actual gentamicin serum concentrations in patient F (70.4 kg) administered 0.6 mg/kg gentamicin. These observed concentrations are below those considered adequate for pneumonia.

DISCUSSION

Gentamicin pharmacokinetics in various hemodialysis regimens have been well studied. However, the research performed to date is limited to gentamicin pharmacokinetics in three times a week sessions using different hemodialysis membranes [5–12]. Presently, one of the major advancements in hemodialysis therapy is the use of SDH hemodialysis as a dialysis modality. These patients dialyze more frequently and use longer treatment times. This treatment has been advocated because it has been demonstrated that increased frequency and longer duration of treatment results in improved patient outcomes [13–17]. To date there is limited data on gentamicin (or any other drug) pharmacokinetics in the SDH hemodialysis population. The aims of this study were to characterize the pharmacokinetics and to model predict an appropriate dose of gentamicin in SDH hemodialysis patients.

Gentamicin is eliminated primarily by the kidney (>95%) in patients with significant renal function. For those with diminished renal function, extracorporeal removal (e.g., hemodialysis) is necessary for elimination. Similar to that reported in other hemodialysis pharmacokinetic studies, gentamicin pharmacokinetics are markedly different between the inter- and intradialytic time periods. We also showed that SDH hemodialysis avidly removes gentamicin from patients. The measured inter- and intradialytic gentamicin clearance rates were also similar to that reported by other investigators [6, 9, 10]. The similar intradialytic gentamicin clearance rates between three times a week dialysis and SDH hemodialysis can be attributed to the differences in dialysate and blood flow rates, time on dialysis, and size of dialysis membrane used in three times a week dialysis and SDH hemodialysis patients. Clearance of drug (or any other solute) is dependent upon many variables, including, but not limited to, the dialysis time, dialyzer size, and flow rates of blood and dialysate. Three times a week dialysis patients are typically exposed to faster blood flow rate and dialysate flow rate (300 to 500 mL/minute and 500 to 800 mL/minute, respectively), larger dialysis membranes (1.6 to 1.8 m^2), and shorter hemodialysis times (3 to 4 hours). The SDH hemodialysis patients in our study were exposed to slower blood flow rate and dialysate flow rate (200 mL/minute and 300 mL/minute, respectively), a smaller dialyzer (0.5 m^2), and a longer hemodialysis time (8 hours).

Of particular interest is the limited gentamicin rebound once the SDH hemodialysis session is completed. In a study of eight patients using three times a week dialysis utilizing F-80 high-efficiency dialysis membranes, greater than 25% rebound occurred [5]. In our present study of SDH hemodialysis, utilizing F50NR high-efficiency dialysis membranes, we observed less than 4% rebound. This difference is most likely attributed to the slower dialysate flow rate and blood flow rate in our trial as compared to that reported earlier. In three times a week dialysis, the hemodialysis removal rate per unit of time of gentamicin from the systemic circulation is faster than the tissue liberation rate of gentamicin into the systemic circulation. Thus, rebound occurs once three times a week dialysis stops. In SDH hemodialysis, the slower dialysate flow rate and blood flow rate and smaller dialyzer result in lower gentamicin removal rate. This, in turn, allows more time for gentamicin to be liberated from the tissues and move into the systemic circulation. Once the SDH hemodialysis session stops, the tissue gentamicin concentration is near equilibration to that of the systemic circulation, therefore, little rebound is observed. The clinical relevance to the lack of gentamicin rebound is that clinicians may inappropriately evaluate an observed gentamicin concentration. Clinicians may assume that gentamicin concentrations will increase to either therapeutic levels, if concentration is low, or increase to toxicity, if levels are high. This, in turn, may lead to changes in gentamicin dose and potential toxicity or loss of efficacy, respectively.

It is not surprising that gentamicin renal clearance correlated strongly to GFR, given that approximately 95% gentamicin is eliminated renally unchanged [21]. Although we found nonsignificant findings in the correlations between gentamicin hemodialysis clearance: Kt/V and gentamicin hemodialysis clearance: URR, the findings were perhaps due to the small sample sizes. The analyses had less than 50% power for each correlation attempted. Three times a week dialysis gentamicin pharmacokinetic studies demonstrated a correlation between gentamicin hemodialysis clearance and dialysis adequacy parameters. [10]

The pharmacokinetic model suggests a gentamicin 2.0 to 2.5 mg/kg intravenous dose to be given after a SDH hemodialysis session to reach therapeutically adequate levels. This will provide serum concentrations between 7.5 μg/mL (peak 1-hour post-dose) and 0.7 μg/mL (trough end of SDH hemodialysis session). These serum concentrations are considered adequate for susceptible organisms [20]. For infectious processes that require higher serum concentrations to assure adequate tissue penetration (e.g., pneumonia), higher doses may be necessary. Given that gentamicin follows first-order pharmacokinetics (i.e., linear), dose increases would be proportional to the desired peak concentration.

Due to the extensive removal by SDH hemodialysis, patients would need full-dose gentamicin administered daily after dialysis days to maintain adequate serum concentrations. This dosing regimen is different than that for three times a week dialysis patients who only require a partial-dose of gentamicin administered after dialysis resulting in lower peaks and/or higher troughs [12, 21]. The difference is attributed to the more frequent dialysis sessions and limited gentamicin rebound in SDH hemodialysis patients. A potential concern of our dosing recommendation is that it is based on a single-dose study. Our patients were not at steady state and the potential for drug accumulation with multiple dosing exists. This effect should be minimal given that dialysis occurs daily.

Aminoglycoside associated otovestibular toxicity and nephrotoxicity are concerns in ESRD patients [22]. Preservation of residual renal function in hemodialysis patients is associated with lower mortality rates [23]. The incidence of toxicity appears to be related to total drug exposure and duration of therapy [24, 25]. Our gentamicin dosing recommendations would allow serum concentrations to fall to 0.7 to 0.8 μg/mL, which is below that considered toxic. Accumulation of gentamicin should not occur with the administration of daily hemodialysis.

CONCLUSION

In summary, gentamicin needs to be given 2.0 to 2.5 mg/kg intravenously after a hemodialysis session in SDH hemodialysis patients to yield adequate serum concentrations. The observed differences in three times a week dialysis and SDH hemodialysis gentamicin pharmacokinetics suggest that other studies in SDH hemodialysis patients need to be conducted utilizing other medications and other hemodialysis membranes.

ACKNOWLEDGMENT

This study was supported by a National Kidney Foundation of North East-New York, Inc., Unrestricted Research Grant Award.

Reprint requests to Harold J. Manley, Pharm. D., BCPS, Assistant Professor of Pharmacy Practice, University of Missouri–Kansas City, 2411 Holmes Street, M3-C19, Kansas City, MO 64108, USA.
E-mail: manleyh@umkc.edu

APPENDIX

Equation 1: Area under the curve (AUC) was calculated by the trapezoidal rule. AUC was calculated for interdialytic time period (AUC_{id}) and intradialytic time period (AUC_{hd}).

Equation 2: Elimination rate constant for interdialytic period (K_{id}) was calculated by

$$K_{id}\ (h^{-1}) = \frac{\ln\ (60 \text{ minutes post-infusion concentration/pre-HD concentration})}{time_{id}}$$

where $time_{id}$ was the time between 60 minutes post-gentamicin infusion and initiation of the next hemodialysis session.

Equation 3: Elimination rate constant for intradialytic period (K_{hd}) was calculated

$$K_{hd}\ (h^{-1}) = \frac{\ln\ (\text{pre-HD concentration/end of HD concentration}}{time_{hd}}$$

where $time_{hd}$ was the time on dialysis.

Equation 4: Volume of distribution (Vd) was calculated as

$$Vd\ (l/kg) = \frac{Dose}{AUC_{id} * K_{id}}$$

The Vd was assumed to be constant throughout the study period.

Equation 5: The renal gentamicin clearance (Cl_R) was calculated as

$$Cl_R\ (mL/min/1.73\ m^2) = \frac{\text{Urine volume} * \text{urine gentamicin concentration}}{AUC_{id}}$$

where urine volume equaled that which was collected over the interdialytic period.

Equation 6: The interhemodialysis (intrinsic) clearance (Cl_{ID}) was calculated as

$$Cl_{ID}\ (mL/min/1.73\ m^2) = Dose/AUC_{id}$$

Equation 7: The amount removed (A) by hemodialysis was calculated as

$$A\ (mg) = (\text{pre-HD concentration} - \text{end of HD concentration}) * Vd$$

Equation 8: The intra-hemodialysis clearance (Cl_{IT}) was calculated as

$$Cl_{IT}\ (mL/min/1.73\ m^2) = A/AUC_{hd}$$

Equation 9: Hemodialysis clearance (Cl_{HD}) was calculated as

$$Cl_{HD}\ (mL/min/1.73\ m^2) = Cl_{IT} - Cl_{ID}$$

Equation 10: Clearance total (Cl_T) was calculated as

$$Cl_T\ (mL/min/1.73\ m^2) = Cl_{ID} + Cl_{IT} + Cl_R$$

Equation 11: Assessment of gentamicin redistribution post-hemodialysis was made for each time point (15, 30, 60 minutes) after hemodialysis and calculated as:

$$\%\ \text{Redistribution} = \frac{\text{X minutes post-HD concentration} - \text{immediate post-HD concentration}}{\text{Immediate post-HD concentration}}$$

Equation 12: Clearances were normalized to a body surface area (BSA) of 1.73 m^2. BSA was determined using the following formula:

$$\left[\frac{ABW\ (kg) \times height\ (cm)}{3600}\right]^{1/2}$$

Equation 13: Elimination half-life was calculated as

$$t_{1/2}\ (hour) = 0.693/K$$

where K equals either K_{id} or K_{hd}.

Equation 14: Estimated glomerular filtration rate (GFR) was calculated from the mean of the following equations:

$$\text{Urea clearance}\ (mL/min/1.73\ m^2) = \frac{\text{urine urea} \times \text{24-hour urine volume}}{BUN \times 1440}$$

where BUN equaled blood urea nitrogen concentration; and

$$\text{Creatinine clearance}\ (mL/min/1.73\ m^2) = \frac{\text{urine creatinine} \times \text{24-hour urine volume}}{\text{Serum creatinine} \times 1440}$$

Hemodialysis adequacy [Kt/V and urea reduction ratio (URR)] were calculated and correlations investigated between hemodialysis adequacy and gentamicin Cl_{IT}. URR was calculated using the following formula

$$URR = 1 - \frac{\text{30-minute post-HD BUN}}{\text{pre-HD BUN}}.$$

Kt/V was calculated using the mean of the following three formulas (equations 15 to 17) [18, 19]

Equation 15:

$$Kt/V = -\ LN\ [(\text{30 minutes post-HD BUN/pre-HD BUN}) - 0.03] + \{[4 - (3.5 \times \text{30 minutes post-HD BUN/pre-HD BUN}] \times UF\ (L)\}/\text{post-HD weight (kg)}$$

Equation 16:

$$Kt/V = -\ LN\ [(\text{30 minutes post-HD BUN/pre-HD BUN}) - (0.008 \times \text{time on HD})] + \{[4 - (3.5 \times \text{30 minutes post-HD BUN/pre-HD BUN}] \times UF\ (L)\}/\text{post-HD weight (kg)}$$

Equation 17:

$$Kt/V = (URR \times 2.3) - 0.284$$

where UF equals ultrafiltration.

REFERENCES

1. United States Renal Data System 1999 Annual Report, Bethesda, The National Institutes of Health, The National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases, 1999.
2. Bloembergen WE, Port FK: Epidemiological perspective in chronic dialysis patients. *Adv Renal Replac Ther* 3:201–207, 1996
3. Vanholder R, Van Loo A, Dhondt AM, *et al*: Influence of uraemia in haemodialysis on host defense and infection. *Nephrol Dial Transplant* 11:593–598, 1996
4. Kahn IH, Catto GRD: Long-term complications of dialysis: Infection. *Kidney Int* 43:S143–S148, 1993
5. Amin NB, Desmond P, Touchette MA, *et al*: Characterization of gentamicin pharmacokinetics in patients hemodialyzed with high-flux polysulfone membranes. *Am J Kidney Dis* 34:222–227, 1999
6. Goetz DR, Pancorbo S, Hoag S, Bloom P: Prediction of serum gentamicin concentrations in patients undergoing hemodialysis. *Am J Hosp Pharm* 37:1077–1083, 1980
7. Dijkmans BA, Mattie H: Predictability of serum concentrations of aminoglycosides after hemodialysis. *Eur J Clin Pharmacol* 33: 179–183, 1987
8. Agarwal R, Toto RD: Gentamicin clearance during hemodialysis: A comparison of high-efficiency cuprammonium rayon and conventional cellulose ester hemodialyzers. *Am J Kidney Dis* 22:296–299, 1993
9. Matzke GR, Halstenson CE, Keane WF: Hemodialysis elimination rates and clearance of gentamicin and tobramycin. *Antimicrob Agents Chemother* 25:128–130, 1984
10. Agarwal R, Cronin RE: Heterogeneity in gentamicin clearance between high-efficiency hemodialyzers. *Am J Kidney Dis* 23:47–51, 1994
11. Christopher TG, Korn D, Blair AD, *et al*: Gentamicin pharmacokinetics during hemodialysis. *Kidney Int* 6:38–44, 1974
12. Amin NB, Padhi D, Touchette MA, *et al*: Characterization of gentamicin pharmacokinetics in patients hemodialyzed with high-flux polysulfone membranes. *Am J Kidney Dis* 34:222–227, 1999
13. Pierratos A, Ouwendyk M, Francoeur R, *et al*: Nocturnal hemodialysis: Three year experience. *J Am Soc Nephrol* 9:859–868, 1998
14. Lockridge RS, Jr, Spencer M, Craft V, *et al*: Nocturnal home hemodialysis in North America. *Adv Ren Replace Ther* 8:250–256, 2001
15. Lacson E Jr, Diaz-Buxo JA: Daily and nocturnal hemodialysis: How do they stack up? *Am J Kidney Dis* 38:228–239, 2001
16. Mohr PE, Neumann PJ, Franco SJ, *et al*: The case for daily dialysis: its impact on costs and quality of life. *Am J Kidney Dis* 37:777–789, 2001
17. Hanly PJ, Pierratos A: Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 344:102–107, 2001
18. Daguirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4:1205–1213, 1993
19. Basile C, Casino F, Lopez T: Percent reduction in blood urea concentration during dialysis estimates Kt/V in a simple and accurate way. *Am J Kidney Dis* 15:40–45, 1990
20. Bauer LA: Clinical pharmacokinetics and pharmacodynamics, in *Pharmacotherapy, A Pathophysiologic Approach*, edited by Dipiro JT, Talbert RL, Yee GC, New Haven, Appleton & Lange, 1999, p 22
21. Aronoff GR, Berns JS, Brier ME, *et al*: Drug prescribing in renal failure, in *Antimicrobial Agents*, Philadelphia, American College of Physicians, 1999, p 42
22. McCormack JP, Jewesson PJ: A critical reevaluation of the "therapeutic range" of aminoglycosides. *Clin Infect Dis* 14:320–339, 1992
23. 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
24. Gilbert DN: Once-daily aminoglycoside therapy. *Antimicrob Agents Chemother* 35:399–405, 1991
25. Nicolau DP, Freeman CD, Belliveau PP, *et al*: Experience with a once-daily aminoglycoside program administered to 2184 adult patients. *Antimicrob Agents Chemother* 39:650–655, 1995