THE ROLE OF MONITORING GENTAMICIN LEVELS IN PATIENTS WITH GRAM-NEGATIVE PERITONEAL DIALYSIS-ASSOCIATED PERITONITIS

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◆ **Background:** There is limited available evidence regarding the role of monitoring serum gentamicin concentrations in peritoneal dialysis (PD) patients receiving this antimicrobial agent in gram-negative PD-associated peritonitis.

◆ **Methods:** Using data collected in all patients receiving PD at a single center who experienced a gram-negative peritonitis episode between 1 January 2005 and 31 December 2011, we investigated the relationship between measured serum gentamicin levels on day 2 following initial empiric antibiotic therapy and subsequent clinical outcomes of confirmed gram-negative peritonitis.

◆ **Results:** Serum gentamicin levels were performed on day 2 in 51 (77%) of 66 first gram-negative peritonitis episodes. Average serum gentamicin levels on day 2 were 1.83 ± 0.84 mg/L with levels exceeding 2 mg/L in 22 (43%) cases. The overall cure rate was 64%. No cases of ototoxicity were observed. Day-2 gentamicin levels were not significantly different between patients who did and did not have a complication or cure. Using multivariable logistic regression analysis, failure to cure peritonitis was not associated with either day-2 gentamicin level (adjusted odds ratio (OR) 0.96, 95% confidence interval (CI) 0.25 – 3.73) or continuation of gentamicin therapy beyond day 2 (OR 0.28, 0.02 – 3.56). The only exception was polymicrobial peritonitis, where day-2 gentamicin levels were significantly higher in episodes that were cured (2.06 ± 0.41 vs 1.29 ± 0.71 , $p = 0.01$). In 17 (26%) patients receiving extended gentamicin therapy, day-5 gentamicin levels were not significantly related to peritonitis cure.

◆ **Conclusion:** Day-2 gentamicin levels did not predict gentamicin-related harm or efficacy during short-course gentamicin therapy for gram-negative PD-related peritonitis, except in cases of polymicrobial peritonitis, where higher levels were associated with cure.

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Peritonitis is a frequent, major complication of peritoneal dialysis (PD) that often results in considerable morbidity, technique failure and mortality (1–3). These adverse clinical outcomes are more common in gram-negative PD-associated peritonitis (4,5). The International Society of Peritoneal Dialysis (ISPD) Guidelines for PD-related Infections (6,7) recommend that initial empiric antibiotic therapy of peritonitis should include gram-negative cover, such as an aminoglycoside. Gentamicin is recommended to be administered intermittently in one exchange daily via the intra-peritoneal (IP) route, such that ongoing effective eradication of gram-negative peritoneal organisms during PD exchanges without gentamicin requires back-diffusion of the antibiotic from the serum into the dialysate for ongoing antimicrobial activity (8). However, excessive systemic absorption of gentamicin into the circulation could potentially lead to ototoxicity (9,10), although other studies have not shown any significant relationship between serum aminoglycoside levels following IP administration and the subsequent risk of ototoxicity (11,12). Some reports have also linked IP gentamicin administration to accelerated loss of residual function (13), although this has not been demonstrated by a large, multi-national registry study (14). Thus, monitoring serum gentamicin levels and adjusting dosages accordingly may or may not be important for maximizing therapeutic efficacy and minimizing toxicity. Nevertheless, the ISPD Guidelines (6) recommend that “monitoring of drug levels for aminoglycosides ... is recommended if toxicity is suspected,” although the evidence underpinning this statement is sparse.

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Indeed, this recommendation is largely based on the observations of one single-center, retrospective study (15), which found that 31 – 56% of patients receiving ISPD-recommended doses of IP gentamicin had day-5 trough gentamicin levels above 2 mg/L, a threshold which has previously been associated with ototoxicity (9). On the other hand, the study also found that day-5 gentamicin levels were similar between patients who did and did not require catheter removal for refractory peritonitis (9). The limited available evidence has fuelled considerable uncertainty regarding the role of monitoring serum gentamicin concentrations in PD patients receiving this antimicrobial agent for PD-related peritonitis (16).

The aim of the present single-center observational cohort study was to investigate the relationship between measured serum gentamicin levels on day 2 following initial empiric antibiotic therapy and subsequent clinical outcomes of confirmed gram-negative peritonitis.

METHODS

PATIENT POPULATION

The cohort study included all patients receiving peritoneal dialysis for end-stage renal failure (ESRF) at Princess Alexandra, Ipswich, Redlands and Logan Hospitals who experienced a gram-negative peritonitis episode between 1 January 2005 and 31 December 2011. Clinical, demographic and treatment data were prospectively recorded on an electronic database and included age, gender, racial origin, cause of primary renal disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus, smoking status, body mass index (BMI), dates and microbiology of peritonitis episodes, PD modality and dialysis fluids used at the time of peritonitis, initial and subsequent antibiotic treatment regimens, and dates and levels of serum aminoglycoside measurements.

Peritonitis was defined as clinical features of peritonitis (abdominal pain or cloudy dialysate) and dialysate leukocytosis (white blood cell count > 100/μL with > 50% neutrophils) (6). Empiric treatment of peritonitis was initiated as soon as possible and consisted of intraperitoneal cephazolin or vancomycin in combination with gentamicin (0.6 mg/kg up to a maximum of 50 mg in one PD exchange each 24 hours). Patients receiving automated peritoneal dialysis (APD) were variably kept on APD or converted to continuous ambulatory peritoneal dialysis (CAPD) for the duration of peritonitis treatment. The day of peritonitis presentation was defined as day 0. Unit protocols recommended random trough serum gentamicin levels be performed on day 2 (after receiving

2 consecutive daily intraperitoneal doses of gentamicin). Gentamicin levels were measured by particle enhanced immuno-turbidimetry on a Beckman Coulter DxC-800 instrument. All patients receiving gentamicin were regularly evaluated for clinical signs or symptoms of ototoxicity. Patients were not administered a further dose of gentamicin unless the serum gentamicin level was below 0.5 mg/L. If the gentamicin level fell below 0.5 mg/L, a further dose of 0.6 mg/kg (maximum dose 50 mg) was administered. Unit protocols also strongly recommended that gentamicin should not be administered for more than 5 days unless recommended by an Infectious Disease Physician. In cases where gentamicin therapy was extended, random trough serum gentamicin levels were performed on a daily basis and further gentamicin was not administered until the level fell below 0.5 mg/L. The unit policy for duration of antibiotic therapy for gram-negative peritonitis was 3 weeks. PD catheters were removed if dialysate effluent remained cloudy after 5 days of antibiotic therapy (6).

The outcomes examined were peritonitis cure, relapse, recurrence, repeat, hospitalization, catheter removal, temporary hemodialysis transfer (in which patients subsequently resumed PD), permanent hemodialysis transfer and patient death. A peritonitis episode was considered “cured” by antibiotics alone if the patient was symptom free, the PD effluent was clear and the episode was not complicated by relapse, catheter removal or death (17). Peritonitis relapse was defined as peritonitis occurring within four weeks of a prior episode in which the dialysate culture yielded the same organism or was sterile (6,7,18). Peritonitis recurrence was defined as peritonitis occurring within four weeks of a prior episode in which the dialysate culture yielded a different organism to that of the original episode (6,7,18). Repeat peritonitis was defined as peritonitis occurring more than 4 weeks after a prior episode in which the dialysate culture yielded the same organism (7,19). Peritonitis-related death was defined as death occurring within 30 days of peritonitis onset (20).

In view of the complexities associated with analysis of multiple events within individuals where the assumption of independence of observations is not appropriate, only the first episodes of gram-negative peritonitis from each individual were included in multivariable analyses.

STATISTICAL ANALYSIS

Results were expressed as frequencies and percentages for categorical variables, mean ± standard deviation for continuous normally distributed variables, and median (interquartile range; IQR) for continuous variables that were not normally distributed. Dichotomous and

categorical data were compared using chi-square tests. Continuous normally distributed data were compared using two-tailed unpaired *t*-tests. Continuous non-normally distributed data were compared using Mann-Whitney tests. The independent predictors of day-2 serum gentamicin levels were assessed by generalized linear model analysis. The independent predictors of the clinical outcomes of peritonitis were determined by multivariable logistic regression using backward stepwise elimination until the most parsimonious model was identified. Day-2 gentamicin levels, administration of gentamicin beyond day 1, age, gender, racial origin, body mass index (BMI), smoking status, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus and PD modality at the time of peritonitis were included in the model as covariates. First-order interaction terms between the significant covariates were examined where appropriate. Data were analyzed using the software packages PASW Statistics for Windows release 18.0 (SPSS Inc., North Sydney, Australia). *P* values less than 0.05 were considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

The overall peritonitis rate during the study period (2005 – 2011) was 0.46 episodes per patient-year (25.9 patient-months per episode). Out of a total of 377 peritonitis episodes in 185 patients, 99 (26%) gram-negative peritonitis episodes were recorded in 66 patients. This equated to a gram-negative peritonitis rate of 0.11 episodes per patient-year. The baseline characteristics of the patients experiencing gram-negative peritonitis episodes are shown in Table 1.

The microbiologic causes of first gram-negative peritonitis episodes during the study period are shown in Table 2. Two-thirds of cases involved single organisms (most commonly *E. coli*, *Pseudomonas* and *Klebsiella*), whilst one-third were polymicrobial. Of the 22 episodes of polymicrobial peritonitis recorded, 12 involved purely gram-negative organisms whilst 10 involved a mixture of gram-negative and gram-positive organisms. In 6 (9%) episodes, gentamicin-resistant gram-negative organisms were isolated from peritoneal dialysis effluent.

Gentamicin therapy was continued for the entire antibiotic treatment course in only 6 (9%) peritonitis episodes. Depending on antimicrobial susceptibilities, gentamicin was changed in the other patients after a median period of three days to amoxycillin (8%), amoxycillin plus clavulanic acid (6%), ampicillin plus sulbactam (3%), cephazolin (9%), cephalexin (17%), ciprofloxacin

(32%), metronidazole (2%), trimethoprim plus sulphamethoxazole (11%) or ticarcillin plus clavulanic acid (3%).

DAY-2 SERUM GENTAMICIN LEVELS

Serum gentamicin levels were performed on day 2 in 51 (77%) of 66 first gram-negative peritonitis episodes. The demographic and clinical characteristics of those who did and did not receive gentamicin levels were comparable (Table 1). Average serum gentamicin levels on day 2 were 1.83 ± 0.84 mg/L (Figure 1). Levels exceeded 2 mg/L in 22 (43%) cases and fell below 0.5 mg/L in 1 (2%) case. No significant independent predictor of higher antibiotic levels was identified.

RELATIONSHIP BETWEEN DAY-2 GENTAMICIN LEVELS AND PERITONITIS OUTCOMES

The complications of first gram-negative peritonitis episodes included relapse (11%), hospitalization (91%), catheter removal (30%) and death (8%). The overall cure rate was 64%. No cases of ototoxicity were observed. Compared with patients who had serum gentamicin levels performed on day 2, those who did not have gentamicin measurements had comparable outcomes and cure rates (Table 3). Day 2 gentamicin levels were not significantly different between patients who did and did not have a complication or cure (Table 4, Figure 2). Using multivariable logistic regression analysis, failure to cure peritonitis was not associated with either day-2 gentamicin level (adjusted odds ratio (OR) 0.96, 95% confidence interval (CI) 0.25 – 3.73) or continuation of gentamicin therapy beyond day 2 (OR 0.28, 95% CI 0.02 – 3.56). Following backward stepwise elimination, the only variables that were independently predictive of lower peritonitis cure rates were older age (OR 1.82 per decade, 95% CI 1.06 – 3.11), male gender (OR 4.87, 95% CI 1.06 – 22.4), peripheral vascular disease (OR 19.0, 95% CI 1.43 – 254) and diabetes mellitus (OR 15.9, 95% CI 1.33 – 192). Cure was not associated with racial origin, BMI, coronary artery disease, cerebrovascular disease, chronic lung disease, smoking status or PD modality. In a sensitivity analysis excluding the single episode of *Bacteroides* peritonitis, day-2 gentamicin levels were not significantly different between patients who were and were not cured (1.87 ± 0.75 vs 1.82 ± 1.00 mg/L, respectively, $p = 0.86$) and did not independently predict failure to cure peritonitis (OR 0.95, 95% CI 0.25 – 3.66).

When polymicrobial gram-negative peritonitis episodes were separately examined, day-2 serum gentamicin levels were significantly higher in those patients who were cured compared to those who were not (2.06 ± 0.41 vs

TABLE 1
 Characteristics of All Patients Experiencing Gram-Negative Peritonitis, Including Those Who Did and Did Not Have Day-2 Serum Aminoglycoside Measurements, at an Australian Center 2005–2011

Characteristic	Total population (n=66)	Day-2 aminoglycoside level measured		<i>P</i> value
		No (n=15)	Yes (n=51)	
Age (years, mean±SD)	58.3±17.1	58.3±15.8	58.3±17.6	1.0
Male gender	31 (47%)	8 (53%)	23 (45%)	0.57
Racial origin				0.49
Asian	8 (12%)	3 (20%)	5 (10%)	
ATSI	1 (2%)	0 (0%)	1 (2%)	
MPI	4 (6%)	0 (0%)	4 (8%)	
Other	3 (5%)	0 (0%)	3 (6%)	
Caucasian	50 (76%)	12 (80%)	38 (58%)	
BMI (kg/m ²)	26.9±5.2	27.0±3.6	26.9±5.6	0.94
ESRF Cause				0.71
Diabetic nephropathy	21 (32%)	3 (20%)	18 (35%)	
Chronic glomerulonephritis	16 (24%)	4 (27%)	12 (18%)	
ADPKD	7 (11%)	3 (20%)	4 (8%)	
Reflux nephropathy	3 (5%)	0 (0%)	3 (6%)	
Renovascular nephrosclerosis	9 (14%)	2 (13%)	7 (14%)	
Other	6 (9%)	2 (13%)	4 (8%)	
Unknown	4 (6%)	1 (7%)	3 (6%)	
Initial dialysis modality				0.64
Hemodialysis	18 (27%)	3 (20%)	15 (29%)	
Peritoneal dialysis	47 (73%)	12 (80%)	35 (69%)	
Renal transplant	1 (2%)	0 (0%)	1 (2%)	
Current smoker	5 (8%)	0 (0%)	5 (10%)	0.21
Hypertension	60 (91%)	15 (100%)	45 (88%)	0.16
Coronary artery disease	25 (38%)	6 (40%)	19 (37%)	0.85
Peripheral vascular disease	19 (29%)	5 (33%)	14 (27%)	0.66
Cerebrovascular disease	15 (23%)	4 (27%)	11 (22%)	0.68
Chronic lung disease	11 (17%)	3 (20%)	8 (16%)	0.69
Diabetes mellitus	23 (35%)	3 (20%)	20 (39%)	0.17
PD modality at time of peritonitis				0.78
APD	7 (11%)	2 (13%)	5 (10%)	
Flush (not yet started PD)	2 (3%)	1 (7%)	1 (2%)	
IPD	9 (14%)	2 (13%)	7 (14%)	
CAPD	48 (73%)	10 (67%)	38 (58%)	
Biocompatible PD fluid	1 (2%)	0 (0%)	1 (2%)	1.0
Icodextrin	5 (7%)	1 (7%)	4 (8%)	1.0
Exchange volume (L/week)				0.13
<56	24 (36%)	6 (40%)	18 (35%)	
56	30 (45%)	4 (27%)	26 (51%)	
>56	12 (18%)	5 (33%)	7 (14%)	

TABLE 1 (cont'd)

Characteristic	Total population (n=66)	Day-2 aminoglycoside level measured		P value
		No (n=15)	Yes (n=51)	
Polymicrobial peritonitis	22 (33%)	5 (33%)	17 (33%)	1.0
Continuation of gentamicin therapy beyond day-2 level	24 (26%)	4 (27%)	20 (39%)	0.66
Gentamicin resistant isolate	6 (9%)	2 (13%)	4 (8%)	0.52

SD = standard deviation; ATSI = Aboriginal and Torres Strait Islander; MPI = Maori and Pacific Islander; BMI = body mass index; ESRF = end-stage renal failure; ADPKD = autosomal dominant polycystic kidney disease; PD = peritoneal dialysis; APD = automated peritoneal dialysis; IPD = intermittent peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis.

TABLE 2
Microbiologic Causes of All First Episodes of
Gram-Negative Peritonitis in PD Patients
at an Australian Center 2005–2011

Organism	Number (%)
<i>Acinetobacter</i>	4 (6%)
<i>Bacteroides</i>	1 (2%)
<i>Citrobacter</i>	2 (3%)
<i>Enterobacter</i>	4 (6%)
<i>E. coli</i>	9 (14%)
<i>Klebsiella</i>	6 (9%)
<i>Pantoea</i>	1 (2%)
<i>Pasteurella</i>	1 (2%)
<i>Pseudomonas</i>	9 (14%)
<i>Serratia</i>	4 (6%)
<i>Stenotrophomonas</i>	3 (7%)
Polymicrobial	22 (33%)
Total	66 (100%)

PD = peritoneal dialysis.

1.29 ± 0.71 , respectively, $p = 0.01$). Similar results were found for pure gram-negative polymicrobial peritonitis (2.13 ± 0.61 vs 1.28 ± 0.68 , $p = 0.11$) and mixed gram-negative and gram-positive polymicrobial peritonitis (2.00 ± 0.23 vs 1.30 ± 0.84 , $p = 0.12$). Although cure rates were too small to permit meaningful multivariable logistic regression analysis, higher day-2 serum gentamicin levels tended to be predictive of a higher rate of cure of polymicrobial gram-negative peritonitis on univariable analysis (OR 12.0, 95% CI 0.98 – 146).

DAY-5 GENTAMICIN LEVELS AND OUTCOMES

Trough serum gentamicin levels were measured on day 5 in 17 (26%) first gram-negative peritonitis episodes.

Figure 1 — Histogram of serum gentamicin levels measured on day 2 in 51 PD patients with first gram-negative peritonitis episodes in an Australian center 2005–2011. PD = peritoneal dialysis.

Average levels were 1.87 ± 0.69 mg/L (minimum 1.1 mg/L, maximum 4 mg/L). Levels exceeded 2 mg/L in 4 (24%) cases. The overall cure rate in this group was 53%. Day-5 serum gentamicin levels did not differ between peritonitis episodes that were cured (1.68 ± 0.41 mg/L, $n = 9$) and those that were not cured (2.08 ± 0.89 mg/L, $n = 8$, $p = 0.26$). Similar results were observed in polymicrobial peritonitis episodes (1.57 ± 0.47 vs 2.55 ± 2.05 mg/L, $p = 0.25$), although numbers were small (6 vs 2).

DISCUSSION

In this single-center observational cohort study, the relationship between measured serum gentamicin level on day 2 following initial empiric antibiotic therapy

TABLE 3
Clinical Outcomes of 66 First Gram-Negative Peritonitis Episodes in PD Patients at an Australian Center During the Period 2005–2011

Characteristic	Total population (n=66)	Day 2 aminoglycoside level measured		P value
		No (n=15)	Yes (n=51)	
Cure with antibiotics	42 (64%)	10 (67%)	32 (63%)	0.78
Relapse	7 (11%)	1 (7%)	6 (12%)	0.57
Recurrence	5 (8%)	0 (0%)	5 (10%)	0.21
Repeat	1 (2%)	0 (0%)	1 (2%)	0.59
Hospitalization				
Number (%)	60 (91%)	15 (100%)	45 (88%)	0.16
Duration (median [interquartile range])	8 (4–11)	8 (2.25–14.5)	8 (4–11)	0.73
Catheter removal	20 (30%)	4 (27%)	16 (31%)	0.73
Temporary hemodialysis	1 (2%)	0 (0%)	1 (2%)	0.59
Permanent hemodialysis	21 (32%)	4 (27%)	17 (33%)	0.63
Death	5 (8%)	1 (7%)	4 (8%)	0.88

PD = peritoneal dialysis.

Results are expressed as number (%) or median days [25th–75th percentile]. Times are expressed as number of days.

TABLE 4
Comparison of Day-2 Serum Gentamicin Levels According to Subsequent Outcome in 51 PD Patients with Gram-Negative Peritonitis Who Had Day 2-Serum Gentamicin Measurements Performed

Outcome	Day-2 gentamicin level according to outcome (mean±SD)		P value
	No	Yes	
Relapse	1.90±0.87 (n=45)	1.35±0.43 (n=6)	0.14
Hospitalization	2.12±0.26 (n=6)	1.79±0.89 (n=45)	0.38
Catheter removal	1.87±0.76 (n=35)	1.75±0.3 (n=16)	0.65
Permanent hemodialysis	1.81±0.74 (n=34)	1.88±1.04 (n=17)	0.76
Death	1.84±0.87 (n=47)	1.78±0.38 (n=4)	0.89
Cure	1.82±1.00 (n=19)	1.84±0.75 (n=32)	0.95

PD = peritoneal dialysis; SD = standard deviation.

and subsequent clinical outcomes of confirmed gram-negative peritonitis was investigated. The study found that failure to cure peritonitis was not associated with

Figure 2 — Box plot of day-2 serum gentamicin levels in 51 PD patients with first episode of gram-negative peritonitis, according to whether or not cure was achieved with antibiotic therapy. PD = peritoneal dialysis.

either day 2 gentamicin level, continuation of gentamicin therapy beyond day 2, or day 5 gentamicin levels in situations where gentamicin therapy was extended. However, sub-group analysis of polymicrobial peritonitis episodes did demonstrate that cure was associated with higher day 2 serum gentamicin levels.

For aminoglycosides, there is a lack of data regarding drug levels and peritonitis outcomes. In a retrospective, single-center observational cohort study of 195 PD patients experiencing peritonitis in whom day-5

gentamicin concentrations were available (15), gentamicin levels were comparable in those with gram-negative peritonitis who were cured and those who required catheter removal (2.13 ± 0.34 vs 1.95 ± 0.11 mg/L, respectively, $p = \text{NS}$). Increasing gentamicin concentrations did not appear to improve cure rates. These results are consistent with the findings of the current series. The lack of correlation between serum gentamicin level and peritonitis in both studies could be explained by the fact that standard microbiological tests (e.g. evaluation of minimum inhibitory concentration (MIC)) did not account for the unique factors of PD peritonitis whereby intraperitoneal antibiotics act primarily locally (6). Consequently, it has been suggested by the ISPD Guidelines that checking of antibiotic levels in peripheral blood should be used for detection of toxicity rather than a proof of efficacy (6). This recommendation was reinforced by a recent study demonstrating high systemic absorption and prolonged plasma elimination of gentamicin in PD patients with peritonitis, potentially leading to systemic drug accumulation and a heightened risk of toxicity (21).

Interestingly, whilst there was no relationship between day-2 gentamicin levels and clinical outcomes in first gram-negative peritonitis episodes overall, day-2 levels were significantly higher in polymicrobial peritonitis episodes that were cured compared to those that were not. This may indicate that gentamicin levels have a greater bearing on the outcomes of more serious gram-negative episodes. Alternatively, since polymicrobial gram-negative peritonitis episodes more commonly involved extended gentamicin therapy and levels beyond day 2 (27% vs 15%), it may be that gentamicin levels become more important during prolonged gentamicin courses. Although no association was observed between day-5 gentamicin levels and gram-negative peritonitis cure in this study, only a minority (26%) of patients were still receiving gentamicin and had day-5 trough levels.

Forty-three per cent of patients in the present study and 31 – 56% of patients from the study of Blunden *et al.* (15) were reported to have serum gentamicin levels exceeding 2 mg/L, a threshold that has previously been associated with ototoxicity (9). However, no ototoxicity was observed in either investigation. This finding may have been attributed to the relatively short period of gentamicin exposure in both studies. Indeed, another pharmacokinetic study demonstrated mean trough serum gentamicin concentrations were more frequently higher than 2 mg/L from the fourth day of treatment (22), although only 4 (25%) of 17 patients in the present study had day-5 gentamicin levels exceeding 2 mg/L. However, there are conflicting findings relating

aminoglycoside levels to ototoxicity. In a prospective study of 47 PD patients treated with continuous IP gentamicin (8 mg/L), Gendeh *et al.* (11) observed mean gentamicin levels of 3.20 ± 1.16 mg/L (range 1.9 – 5.3 mg/L) at the end of 30 exchanges with no evidence of ototoxicity. In contrast, another investigation of 19 PD patients reported that clinical ototoxicity occurred even in the context of low serum gentamicin levels (10). Another study has not shown any significant relationship between serum aminoglycoside levels following IP administration and the subsequent risk of ototoxicity (12). Serum aminoglycoside levels have also been linked to accelerated loss of residual renal function (13), although this has not been demonstrated by a recent large, multi-national registry study (14). Further study in this area is warranted.

The present study has several limitations. First, the relatively small sample size meant that the possibility of a type 2 statistical error could not be excluded. Second, gentamicin courses in the study were relatively short (74% did not continue beyond day 2) thereby limiting meaningful evaluation of levels with longer courses. Consequently, the possibility that measuring gentamicin levels later than day 2 in the course of a peritonitis episode may be more strongly related to outcome could not be discounted. Third, the non-randomized design of the study meant that there was a possibility that the results were confounded by indication bias, even though no differences in baseline characteristics were observed between those who did and did not have gentamicin levels. Fourthly, whilst clinicians routinely monitored patients receiving intraperitoneal gentamicin for symptoms and signs of gentamicin ototoxicity, more sensitive investigations, (such as caloric tests and electronystagmography), were not performed, such that mild ototoxicity may have been missed. Residual renal function was also not measured around the time of the peritonitis episodes, such that gentamicin levels could not be related to changes in this parameter. However, our group has previously demonstrated in a large, multi-national registry study that empiric treatment of peritonitis with aminoglycosides was not associated with an adverse effect on residual renal function in PD patients (14).

In conclusion, this single center observational cohort study showed that day-2 trough gentamicin levels did not predict gentamicin-related harm or efficacy during short-course gentamicin therapy for gram-negative PD-related peritonitis, except in cases of polymicrobial peritonitis. Further studies investigating the role of gentamicin levels during more prolonged (≥ 5 days) gentamicin courses are warranted.

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