Single UK centre experience on the treatment of PD peritonitis—antibiotic levels and outcomes

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Abstract

Background. There are few studies of the pharmacokinetics of vancomycin and gentamicin in peritoneal dialysis (PD) patients and the influence of antibiotic concentrations on treatment outcome. Concerns about resistance to ceftazidime and potential of aminoglycoside toxicity make the choice of empiric antibiotic difficult.

Methods. We retrospectively collected data from 613 patients on PD between 1 June 2002 and 31 December 2005. During this time, we adopted a protocol that minimized aminoglycoside exposure to patients with residual renal function and carefully monitored serum antibiotic concentrations.

Results. There were no statistical differences in mean day-5 vancomycin concentrations for continuous ambulatory peritoneal dialysis (CAPD) vs automated peritoneal dialysis (APD) and for anuric vs not-anuric patients. However, low levels (<12 mg/l) were recorded for 12.8% CAPD and 15% APD patients. These remained low at day 10 in 16% patients (25% if not anuric) despite incremental dosing. Vancomycin concentration did not predict cure or relapse of Gram-positive or culture-negative peritonitis. Gentamicin concentration (>2 mg/l in >50% patients) did not predict outcome of Gram-negative and culture-negative peritonitis. Moreover, cure rates were the same irrespective of whether gentamicin was continued for 14 days or was switched to ceftazidime after 5 days.

Conclusion. We have confirmed that the International Society for Peritoneal Dialysis (ISPD) dosing guideline for vancomycin in CAPD and APD patients produces adequate serum concentrations of the antibiotics in the vast majority. However, large incremental dosing of vancomycin is needed if day-5 levels are low; especially for not-anuric patients. Whilst evidence of gentamicin toxicity in PD remains controversial, ISPD dosing regimen resulted in high levels for >50% patients. High gentamicin concentrations did not correlate with treatment success, but switching gentamicin to ceftazidime at day 5 appeared safe and limited aminoglycoside exposure. Increasing vancomycin and gentamicin concentrations do not appear to improve cure rates and alternative strategies (such as combination treatment) should be considered for future research.

Keywords: ceftazidime; gentamicin; outcomes; peritoneal dialysis; peritonitis; vancomycin

Introduction

Peritoneal dialysis (PD) peritonitis remains the most important complication despite numerous advances such as the use of disconnect and flush before fill systems [1,2]. Appropriate use of antibiotics remains central to the treatment of peritonitis and the International Society for Peritoneal Dialysis (ISPD) published guidelines in 2000 [3] that were updated in 2005 [4]. However, these were based on small pharmacokinetic studies in CAPD and little data exist of the pharmacokinetics of vancomycin or gentamicin in APD. We have retrospectively analysed the management and outcome of 534 new episodes of peritonitis that followed the ISPD dosing schedules to determine the proportion of patients that had low vancomycin or high gentamicin concentrations on day 5 and 10. We have attempted to correlate treatment outcomes with the achieved antibiotic concentrations.

The ISPD guidelines have also suggested that prolonged treatment of aminoglycosides should be avoided because of potential nephrotoxicity [3,4]. Alternative therapy suitable for the treatment of Gram-negative organisms include IP ceftazidime [5–10] but this might not be suitable as empiric treatment if the prevalence of multi-resistance to cephalosporins is high. We adopted a policy to switch gentamicin to ceftazidime in patients with residual renal function (RRF) after microbiological confirmation of sensitivity was available (day 5 of peritonitis). We wish to report the incidence of...
Methods

Patient selection

Data were collected retrospectively from all patients on the PD program at Bart’s and the London NHS Trust (London, UK) between 1 June 2002 and 31 December 2005. This 43-month study period represents over 10,000 patient-months of PD. All CAPD patients were on a disconnect PD system (MiniSolo or UV Compact, Baxter Healthcare, Northants, UK or StaySafe, Fresenius, Bad Humburg, Germany). All APD patients used the HomeChoice machine (Baxter Healthcare, Northants, UK). Icodextrin was increasingly used in our unit during the study period (46% in 2002, 64% in 2003, 69% in 2004 and 82.6% in 2005). Amino acid-based dialysate fluid (Nutrineal) was used only in small numbers of patients (2 in 2002 increasing to 11 patients in 2005). Our unit only started to prescribe Physioneal® (biocompatible twin chamber dialysis system containing glucose solution at neutral pH and which is low in glucose degradation products) in 2004 for incident patients (used in 11% of all PD patients in 2004 and 22.8% in 2005).

Diagnosis and culture of PD effluent

Diagnosis of peritonitis was based on symptoms (one or more of abdominal pain, fever or cloudy dialysate) and microscopy of PD effluent (showing >100 wbc/mm³ of which >50% were neutrophils). Gram stain and culture were performed in all cases. Effluent was obtained from CAPD and APD patients after a minimum of 2 h dwell. Samples were sent immediately for microbiological assessment that included Gram stain, microscopy for cell count and culture on Blood and MacConkey agar in CO2 at 37°C for 48 h. Two 10 ml samples were also inoculated into aerobic and anaerobic blood culture broth (Bact/ALERT Biomerieux Inc. Durham NC). This was continually monitored for bacterial growth using the automated Bact/Alert system for 4 days. We routinely tested cultures using the disc-diffusion method according to the National Committee for Clinical Laboratory Standard to determine antibiotic sensitivities.

Antibiotic protocol

Empirical treatment for peritonitis in our unit included IP vancomycin with the dose modified for urine output (anuria defined as urine output <200mls/d) and corrected for body weight. This was administered on presentation (single dose of 25 mg/kg rounded to the nearest 500 mg for anuric patients but increased by 25% if not anuric). Patients also received daily IP gentamicin (0.6 mg/kg once a day for anuric patients but increased by 25% if not anuric) for 5 days or until culture results are known. Patients were told to leave the PD bag with the first dose antibiotic intraperitoneally for a minimum of 6 h. Subsequent doses of gentamicin were administered intraperitoneally into the longest dwell bag (for at least 8 h). If APD patients were normally ‘dry’, they were instructed to administer antibiotics into a 1 l last fill.

Treatment was subsequently adjusted according to organism and sensitivity (Table 1). We have reported serum antibiotic concentrations only for patients who continued on PD to eliminate the confounding effects of HD clearance and dosing.

The day-5 antibiotic dose of vancomycin was titrated according to trough serum vancomycin concentration. The previous vancomycin dose was increased by 500 mg if the serum concentration on day 5 was <12 mg/l, continued unchanged if serum concentration was between 12–25 mg/l and the dose reduced by 500 mg if the serum concentration was >25 mg/l.

If gentamicin was continued after day 5, dose was titrated against trough serum concentration to minimize potential for toxicity. If serum concentration was <2 mg/l, the dose of gentamicin was unchanged but was reduced by 10 mg if >2 mg/l. If the trough concentration was >3 mg/l, day-5 dose was omitted and maintenance dose reduced by 10 mg.

Total antibiotic duration was 14 days for new episodes of peritonitis and 21 days for relapses.

Data collection

Outcomes for all episodes were classified as cured, relapsed or non-resolving. Primary cure was defined as an episode of peritonitis where the catheter remained in situ and symptoms and signs resolved. Relapse was recorded as the outcome if peritonitis recurred (with the same organism as the original infection or culture-negative) within 28 days of completing the previous course of antibiotic. If PD effluent remained cloudy despite 5 days of treatment, the PD catheter was removed and the case was defined as non-resolving. In a small minority of cases, there was a clinical presentation that suggested bowel perforation. PD catheters would have been removed during laparotomy and the case was defined as non-resolving.

Vancomycin and gentamicin assay

The Abbott TDX system (IL, USA) for antibiotic assays was used to measure serum concentrations of vancomycin and gentamicin. Trough concentrations were measured on days 5 and 10 (if the relevant antibiotic was continued past day 5).
We analysed the data defining low vancomycin levels to be <12 μg/l.

**Statistical analysis**

The cure rates between specified groups of patients (CAPD vs APD and anuric vs not anuric) were compared using chi-square tests. Day-5 vancomycin and gentamicin concentrations in CAPD vs APD and anuric vs not-anuric patients were compared using Student's t-test. Bonferroni correction was employed where relevant for multiple analyses.

**Results**

**Patient characteristics**

There were 613 patients on PD between 1 June 2002 and 31 December 2005. During the study period, 301 patients developed an episode of peritonitis. There were 267 patients that developed peritonitis whilst undergoing CAPD vs 120 patients on APD (86 patients suffered peritonitis undergoing both CAPD and APD). The demographics of these patients are shown in Table 2.

A total of 534 new episodes of peritonitis were recorded during the study period, representing a peritonitis rate for patients on CAPD of 1:17.7 and on APD of 1:23.6 patient-months. Overall, peritonitis rate over this period was 1:19.4 patient-months.

The frequency of different organisms is listed in Table 2. Gram-negative organisms were identified in 137 episodes (23.0% of all cases; 22.0% in CAPD and 25.7% in APD). Gram-positive organisms were cultured in 283 episodes (47.5% of all peritonitis; 49.2% vs 43.3% in CAPD vs APD peritonitis respectively). There were 166 episodes (27.9%) of culture-negative peritonitis (27.8% of CAPD peritonitis and 28.1% of APD peritonitis).

**Vancomycin concentrations**

Day-5 serum vancomycin concentration data were available in 130 anuric and 144 not-anuric patients on CAPD and 56 and 44 patients on APD. Day-10 vancomycin concentrations were available from 110 anuric, 131 not-anuric CAPD and 43 anuric, 40 not-anuric APD patients. The mean doses of vancomycin administered on day 1 to CAPD patients were 2.00 ± 0.02 g for anuric and 2.35 ± 0.02 g for not-anuric. The mean dose given to APD patients on day 1 were 2.00 ± 0.04 and 2.36 ± 0.03 g (anuric vs not anuric). The resulting day-5 and -10 serum vancomycin concentrations are shown in Figure 1 (mean and quartile ranges included). There were no statistically significant differences between any of the groups.

The proportion of anuric CAPD, not-anuric CAPD, anuric APD and not-anuric APD patients with low day-5 vancomycin levels (<12 mg/l) were: 9.2, 16.0, 16.1 and 13%, respectively. After incremental dosing, the proportion of CAPD patients that continued to have low vancomycin concentrations on day 10 were 0% (anuric) and 21% (not anuric). The proportion of APD patients that continued to have low levels were 13% (anuric) and 25% (not anuric). Although the proportions of not-anuric patients with persistently low vancomycin concentrations were higher, this did not achieve statistical significance.

![Fig. 1. Trough serum vancomycin concentrations at days 5 and 10.](image-url)
Gentamicin concentrations

Data on day-5 gentamicin concentrations were available for 78 anuric, 60 not-anuric CAPD and 35 anuric, 22 not-anuric APD patients. The mean daily gentamicin doses that were administered between days 1–5 were 40.3 ± 0.9 vs 51.8 ± 1.4 mg (anuric vs not anuric) in CAPD and 40.0 ± 1.5 and 53.2 ± 2.0 mg in APD. The mean trough serum gentamicin concentrations are shown in Figure 2. There were no statistically significant differences between any groups.

Day-5 gentamicin levels were above 2 mg/dl in 52.6% of anuric and 55.7% of not-anuric CAPD patients. High day-5 serum trough concentrations of gentamicin were also experienced in 31.4 and 54.5% of anuric and not-anuric APD patients, respectively.

Outcome of peritonitis in CAPD vs APD patients

The primary cure of CAPD and APD patients with peritonitis was 77.2 and 74.7%, respectively. The cure rates were similar irrespective of residual renal function. Although cure rate for not-anuric APD patients with Gram-negative peritonitis was lower than for CAPD patients, this was not statistically significant by chi-square testing (Table 3).

Correlation of antibiotic concentration with peritonitis outcome

Day-5 gentamicin levels were similar in patients that were cured of Gram-negative peritonitis compared with those that required catheter removal for non-resolution (2.13 ± 0.34 vs 1.95 ± 0.11 mg/l, P = NS). This was also true for culture-negative peritonitis (day-5 gentamicin concentrations of cured vs catheter removal groups were 2.21 ± 0.20 vs 2.26 ± 0.16 mg/l, P = NS). Similarly, vancomycin concentrations did not correlate with the outcomes after Gram-positive or culture-negative peritonitis. If the patients with these types of peritonitis were grouped to vancomycin concentrations: <12, 12–24 and >24 mg/l, the cure rates were 77.9, 74.2 and 75.0%, respectively (P = NS), Table 4.

Outcome peritonitis treated with gentamicin vs ceftazidime

We had complete data for 111 episodes of Gram-negative peritonitis during the study period. There were no episodes of peritonitis from non-pseudomonal Gram-negative organisms (enterobacteriaceae) with extended β-lactamase activity although 8 cases of pseudomonas peritonitis were resistant to ceftazidime. There were 42 CAPD and 23 APD peritonitis episodes that were treated solely with gentamicin and primary cure occurred in 50.0 and 52.2%, respectively, P = NS (Table 3). There were 33 and 13 not-anuric CAPD and APD patients with Gram-negative peritonitis (treated with a combination of Ceftazidime and gentamicin) and cure was 57.6 and 33.8%, respectively. The differences in cure rates of the two different treatment protocols (switch or no switch of gentamicin at day 5), when CAPD and APD data were pooled, were 50.7% for gent-only vs 56.5% for gent-ceftazidime, P = NS by chi-square analysis.

Table 3. Outcome of PD peritonitis according to organism

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<td>Cure rate</td>
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<td></td>
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<td>Not anuric</td>
<td>Anuric</td>
<td>Not anuric</td>
<td>Anuric</td>
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<tr>
<td>Gram +ve</td>
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<tr>
<td>Staph. A</td>
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<td>94</td>
<td>82.1</td>
<td>95</td>
<td>78.7</td>
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<tr>
<td>Coag. neg. Staph</td>
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<td>50.0</td>
<td>14</td>
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<tr>
<td>Others</td>
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<td>87.0</td>
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<td>90.0</td>
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<tr>
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<tr>
<td>Pseudomonas</td>
<td>75</td>
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<td>88.6</td>
<td>35</td>
<td>60.0</td>
</tr>
<tr>
<td>Others</td>
<td>50</td>
<td>42</td>
<td>57.6</td>
<td>33</td>
<td>52.2</td>
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<tr>
<td>Culture neg.</td>
<td>75.5</td>
<td>40</td>
<td>85.9</td>
<td>64</td>
<td>100</td>
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Table 4. Cure rate according to trough serum vancomycin concentrations at day 5

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<thead>
<tr>
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<th>&lt;12 mg/l</th>
<th>12–24 mg/l</th>
<th>&gt;24 mg/l</th>
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<tbody>
<tr>
<td>Gram +ve peritonitis</td>
<td>85.3%</td>
<td>77.9%</td>
<td>68.4%</td>
</tr>
<tr>
<td>No growth peritonitis</td>
<td>54.5%</td>
<td>79.6%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Combined</td>
<td>77.9%</td>
<td>74.2%</td>
<td>75.0%</td>
</tr>
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No statistical differences were found by chi-square analysis with three categories (defined as above) or when the second and third columns were combined (i.e. <12 vs >12 mg/l).
There were 40 and 14 episodes of culture-negative peritonitis in anuric patients on CAPD and APD, respectively. These were treated with vancomycin and gentamicin in accordance to our protocol and primary cure rate was 77.5 and 100% (P = NS). The cure rate of culture-negative peritonitis in not-anuric PD patients was 85.9 vs 79.3%, P = NS (for 64 CAPD and 29 APD, respectively). If the CAPD/APD and Gram-negative/culture-negative groups were combined, the cure rate of anuric PD patients (treated with vancomycin and gentamicin) was 65.5 vs 74.8% in not-anuric patients (treated with a combination of vancomycin and gentamicin/ceftazidime). This difference was not statistically significant.

Discussion

Our study demonstrated that the dosing schedule recommended by the ISPD for vancomycin achieved adequate serum antibiotic concentrations for the 88.2% of CAPD and 85% of APD patients. We defined serum vancomycin concentrations <12 mg/l to be low because Gram-positive organisms are generally susceptible to vancomycin with MIC <4 mg/l [11] and pharmacokinetic studies suggest that the serum:PD effluent concentration of vancomycin is 3:1 [7]. A dose increment of 500 mg appeared insufficient in a significant number of patients (~25% in patients with RRF) that had low vancomycin levels on day 5. The reason for disparate serum vancomycin concentrations in PD peritonitis patients despite standardized dosing was unclear. We were unable to determine if differing peritoneal transport characteristics and dialysis clearance that is altered during infection might be the explanation.

Day-5 serum vancomycin concentrations did not predict treatment outcome. The cure rate for patients with vancomycin concentrations below 12 mg/l was similar to those with higher day-5 concentrations. Similarly, delivering very high concentrations of vancomycin (>25 mg/l on day 5) did not appear to be beneficial although one might expect a lower relapse rate through better treatment of biofilm colonization [12]. Our results are different from those published by Mulhern et al. [13] who demonstrated a positive correlation between serum vancomycin concentrations and cure rate in 31 patients. Despite the absence of any correlation, we believe antibiotic monitoring is still helpful to minimize potential toxicity particularly if aminoglycosides are also used for PD peritonitis.

We have shown that the ISPD dosing recommendation for gentamicin delivers a mean trough serum concentration at day 5 of 2.15 ± 0.09 and 2.27 ± 0.13 mg/l (anuric vs not anuric) CAPD and 1.91 ± 0.11 and 2.26 ± 0.25 mg/l (anuric vs not anuric) APD patients. There is no consensus to what constitutes sub-therapeutic trough serum gentamicin levels, but using a threshold of 2 mg/l, we demonstrated that high trough levels were experienced in between 31–56% of patients. Although some studies did not demonstrate gentamicin nephrotoxicity [14], and some experts believe that the newer formulations of vancomycin are less toxic [15], there remains the potential that the synergism of vancomycin with aminoglycosides can cause ototoxicity [16]. Unfortunately, our study was not designed to determine if toxicity occurred.

Ceftazidime has been frequently suggested to be an alternative to aminoglycosides but high prevalence of β-lactamase activity, as reported in Hong Kong [17] can be a problem if adopted as empiric blind therapy. We report that minimizing the gentamicin exposure by switching to ceftazidime on day 5 when antibiotic sensitivity is known appeared an effective strategy; cure rates were similar irrespective of whether the patient was switched to ceftazidime or continued on gentamicin. Of course, it should be emphasized that we are not directly comparing the efficacy of gentamicin vs ceftazidime (an RCT has already been published) [18]. The confounding relationship between anuria and the use of gentamicin and the size of our study are the weaknesses of our report of our clinical practice. It is also a concern that the cure rate of our Gram-negative peritonitis is low. Sub-therapeutic gentamicin concentration did not appear to be the cause (trough serum gentamicin concentration at day 5 of the Gram-negative peritonitis that cleared was similar to those that were not cured). Instead, our cure rate might be a reflection of our low threshold to remove the PD catheter (on days 3–5). Nevertheless, it is possible that other unidentified factors might limit the relevance of our results to other units.

In summary, we have generally validated the ISPD dosing guideline for vancomycin and gentamicin in both CAPD and APD patients. However, there is suggestion that incremental dosing of vancomycin should be greater than 500 mg if day 5 trough levels are low. We have also shown that these guidelines resulted in high trough serum gentamicin concentration for a significant number of patients. The potential synergy with vancomycin to cause nephro- and oto-toxicity should be explored in further studies. Accepting important limitations of our study, there was no correlation between serum antibiotic concentrations and peritonitis outcome. Switching gentamicin to ceftazidime after culture results were available also appeared safe and minimized the risk of aminoglycoside toxicity.

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References


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