INFLUENCE OF DIFFERENT PERITONEAL DIALYSIS FLUIDS ON THE *IN VITRO* ACTIVITY OF CEFEPIME, CIPROFLOXACIN, ERTAPENEM, MEROPENEM AND TOBRAMYCIN AGAINST *ESCHERICHIA COLI*

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◆ **Background:** Peritonitis is a major problem among patients on peritoneal dialysis (PD). The influence of diverse PD fluids on the activity of frequently used antibiotics has been insufficiently investigated. Thus, the present study set out to investigate the impact of different PD fluids on the activity of cefepime, ciprofloxacin, ertapenem, meropenem, and tobramycin against *Escherichia coli*.

◆ **Methods:** Time-kill curves in 4 different PD fluids (Dianeal PDG4, Extraneal, Nutrineal PD4 and Physioneal 40, all Baxter Healthcare Corp., Deerfield, IL, USA) were performed over 24 hours with 4 different concentrations ($1 \times$ minimum inhibitory concentration [MIC], $4 \times$ MIC, $8 \times$ MIC, $30 \times$ MIC) of each antibiotic evaluated and without antibiotics as control. Cation-adjusted Mueller Hinton broth (CA-MHB) was used as comparator solution.

◆ **Results:** In all PD fluids investigated, bacterial growth and antimicrobial activity of all antibiotics tested was significantly reduced compared with the CA-MHB comparator solution. Except at high concentrations of $30 \times$ MIC, cefepime, ertapenem and meropenem demonstrated a strongly reduced activity in all PD fluids investigated. Ciprofloxacin and tobramycin were highly active and bactericidal in all PD fluids and demonstrated dose-dependent activity.

◆ **Conclusion:** The antimicrobial activity of cefepime, ertapenem and meropenem is limited or even nullified in certain PD fluids *in vitro*, whereas ciprofloxacin and tobramycin show excellent activity. The choice of PD fluids can impact the activity of antimicrobial agents and might influence microbiological outcome. Further studies are required to verify the clinical relevance of our findings.

Escherichia coli belongs to the causative organisms isolated most frequently with a prevalence up to 10% in patients with PD-related peritonitis (PDRP) (1,2). According to the recommendations of the International Society for Peritoneal Dialysis (ISPD), empirical antimicrobial treatment of PDRP should cover both gram-positive and gram-negative bacteria. For gram-negative coverage, aminoglycosides, carbapenems or fourth generation cephalosporins are recommended (3). Further, quinolones may be regarded as an acceptable alternative in consideration of local resistance patterns (3). In general, intraperitoneal (IP) application of antibiotics is recommended for the management of PDRP due to higher target site concentrations, less gastrointestinal side effects, and improved compliance (3,4). Despite frequent IP usage among patients on PD, little information is available on the influence of diverse PD fluids (PDFs) on the activity of antimicrobial agents. Thus, the present study set out to investigate the impact of different commercially available PDFs on the activity of cefepime, ciprofloxacin, ertapenem, meropenem, and tobramycin against *E. coli*.

MATERIAL AND METHODS

BACTERIAL STRAIN AND SUSCEPTIBILITY TESTS

E. coli (ATCC 25922) was used in this study. The minimal inhibitory concentrations (MICs) determined by broth microdilution in cation-adjusted Mueller Hinton broth (CA-MHB) were 0.06 µg/mL for cefepime, 0.008 µg/mL for ciprofloxacin, 0.008 µg/mL for ertapenem, 0.03 µg/mL for meropenem, and 0.5 µg/mL for tobramycin.

ANTIBIOTICS AND GROWTH MEDIA

Four commercially available PDFs with different compositions, namely Dianeal PDG4 (1.36% glucose), Extraneal (75 g/2,000 mL icodextrin), Nutrineal PD4 (1.1% amino acids) and Physioneal 40 (2.27% glucose) (all Baxter Healthcare Corp., Deerfield, IL, USA) were used. The pH of these solutions was adjusted to 7.30–7.50 with NaHCO₃ to simulate the

Perit Dial Int 2016; 36(6):662–668 epub ahead of print: 28 Sept 2016
<https://doi.org/10.3747/pdi.2015.00161>

KEY WORDS: Antibiotics; infection; peritoneal dialysis solutions; peritonitis; time-kill curves.

Peritonitis remains a clinically important complication among patients on peritoneal dialysis (PD), highlighting the need for improved therapeutic strategies. Among gram-negative bacteria,

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Received 9 July 2015; accepted 22 February 2016.

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physiological pH after a 4–6 h IP dwell (5–7). Cation-adjusted Mueller Hinton broth was used as comparator solution. Cefepime (Sandoz, Kundl, Austria), ertapenem (Merck Sharp & Dohme, Clermont-Ferrand, France), and meropenem (Venus Pharma, Werne, Germany) were obtained in form of dry powders; ciprofloxacin (Fresenius Kabi Norge AS, Halden, Norway) and tobramycin (B. Braun Medical S. A., Barcelona, Spain) were obtained as 2 mg/mL and 1 mg/mL infusion solutions, respectively. All antibiotics were diluted in sterile distilled water and stored at -80°C until use.

TIME-KILL ASSAYS

Time-kill curves were performed in the diverse PDFs and in CA-MHB as comparator solution. Bacteria were incubated overnight on 5% sheep blood agar plates at 36°C , then suspended in 0.9% sterile saline to a concentration equivalent to a 0.5 McFarland standard. The final inoculum of $\sim 5 \times 10^5$ colony-forming units (CFU)/mL was obtained by dilution in working fluids. Tubes (10 mL) with different PDFs or CA-MHB containing the final inoculum were incubated on an orbital shaker for 2 hours at 36°C . Following this, antibiotics were added to achieve final concentrations corresponding to $1 \times \text{MIC}$, $4 \times \text{MIC}$, $8 \times \text{MIC}$, and $30 \times \text{MIC}$, respectively. Control assays without antibiotics were run in all PDFs and in the CA-MHB comparator solution. Samples were taken at -2, 0 (immediately after antibiotic addition), 2, 4, 6, 10, and 22 hours and bacterial counts were determined using 10-fold dilutions plated on 5% sheep blood agar plates. Time-kill curves for each antibiotic concentration were obtained by plotting $\log_{10}$ CFU/mL versus time. Bactericidal activity was defined as a reduction of $\geq 3 \log_{10}$ CFU/mL compared with initial inoculum (5). The definition of a bacteriostatic effect was set as a difference of less than $\pm 1 \log_{10}$ CFU/mL compared with the initial inoculum.

STATISTICS

Results were analyzed and plotted using GraphPad Prism version 5 (GraphPad Software, San Diego, CA, USA). Two-way ANOVA tests with bonferroni post-tests were performed to compare the different solutions and antibiotic concentrations with CA-MHB curves at each time point investigated. Further, the CFU/mL obtained from antibiotic-containing PDFs were compared with bacterial counts in PDF controls at each time point.

RESULTS

Time-kill curves are outlined in Figures 1–5. In all PDFs investigated, bacterial growth was significantly reduced compared with the CA-MHB comparator solution ($p < 0.001$). Further, the antimicrobial activity of all antibiotics tested was reduced. Cefepime was bactericidal in CA-MHB at high concentrations of $30 \times \text{MIC}$ but not at lower concentrations or in any PDF investigated. Applied at a concentration of $30 \times \text{MIC}$, after 22 hours, the reduction in CFU/mL was $2.03 \log_{10}$ CFU/mL in Physioneal 40, $1.78 \log_{10}$ CFU/mL in Nutrineal PD4, $1.11 \log_{10}$

Figure 1 — Time-kill curves in CA-MHB and in 4 different peritoneal dialysis fluids at concentrations of cefepime equal to $1 \times \text{MIC}$, $4 \times \text{MIC}$, $8 \times \text{MIC}$ and $30 \times \text{MIC}$. The dotted line shows the time of antibiotic addition, which was done directly before bacterial counts. The area in grey represents the time of dwell periods frequently used in clinical practice. CA-MHB = cation-adjusted Mueller Hinton broth; CFU = colony forming units; MIC = minimum inhibitory concentration.

CFU/mL in Dianeal PDG4, and $0.19 \log_{10}$ CFU/mL in Extraneal (Figure 1). Ertapenem was bactericidal in CA-MHB but not in any PDF investigated. Applied at a concentration of $30 \times \text{MIC}$, after 22 hours the reduction in CFU/mL was $2.42 \log_{10}$ CFU/mL in Physioneal 40, $1.47 \log_{10}$ CFU/mL in Dianeal PDG4, $1.43 \log_{10}$ CFU/mL in Nutrineal PD4, and $0.95 \log_{10}$ CFU/mL in Extraneal (Figure 3). Meropenem was bactericidal in CA-MHB but not in any PDF investigated. Applied at a concentration of $30 \times \text{MIC}$, after 22 hours, the reduction in CFU/mL was $2.99 \log_{10}$ CFU/mL in Physioneal 40, $1.58 \log_{10}$ CFU/mL in Dianeal PDG4, $1.45 \log_{10}$ CFU/mL in Nutrineal PD4, and $0.61 \log_{10}$ CFU/mL in Extraneal (Figure 4). Thus, in Physioneal 40, meropenem achieved a reduction barely below the limit for bactericidal activity. Ciprofloxacin showed bactericidal activity in CA-MHB and in all PDFs at high concentrations but only in Physioneal 40 at any concentration evaluated. In Dianeal PDG4 and Extraneal, bactericidal activity was present at concentrations of $4 \times \text{MIC}$ or above. In Nutrineal PD4, a concentration of $8 \times \text{MIC}$ achieved a difference of $2.95 \log_{10}$ CFU/mL, and bactericidal activity was only shown at a concentration of $30 \times \text{MIC}$ (Figure 2). Ciprofloxacin showed bactericidal activity in CA-MHB and Physioneal 40 at any concentration evaluated,

Figure 2 — Time-kill curves in CA-MHB and in 4 different peritoneal dialysis fluids at concentrations of ciprofloxacin equal to 1 × MIC, 4 × MIC, 8 × MIC and 30 × MIC. The dotted line shows the time of antibiotic addition, which was done directly before bacterial counts. The area in grey represents the time of dwell periods frequently used in clinical practice. CA-MHB = cation-adjusted Mueller Hinton broth; CFU = colony forming units; MIC = minimum inhibitory concentration.

in Dianeal PDG4 and Extraneal at concentrations of 4 × MIC or above, and in Nutrineal PD4 at a concentration of 30 × MIC (Figure 2). Tobramycin demonstrated bactericidal activity in CA-MHB and in each PDF at any concentration evaluated and reduced the bacterial counts under the detection limit within 2 to 22 hours. The velocity of bacterial killing was highest in the amino acid-containing PDF Nutrineal PD4 (Figure 5). In clinical practice, Dianeal PDG4, Nutrineal PD4, and Physioneal 40 are usually applied IP for short dwells lasting 4 – 6 hours, whereas Extraneal is applied for longer dwells. Therefore, the reduction of CFU/mL during a time period of 6 hours (for Dianeal PDG4, Nutrineal PD4, and Physioneal 40) and 10 hours (for Extraneal) after addition of antibiotics is presented for 2 different drug concentrations in each PDF tested in Table 1.

DISCUSSION

In the present study, the growth of *E. coli* as well as the antimicrobial activity of cefepime, ertapenem, and meropenem in different PDFs was reduced or even nullified compared with CA-MHB, whereas ciprofloxacin and tobramycin retained excellent activity. A reduced growth of bacteria and yeasts in

Figure 3 — Time-kill curves in CA-MHB and in 4 different peritoneal dialysis fluids at concentrations of ertapenem equal to 1 × MIC, 4 × MIC, 8 × MIC and 30 × MIC. The dotted line shows the time of antibiotic addition, which was done directly before bacterial counts. The area in grey represents the time of dwell periods frequently used in clinical practice. CA-MHB = cation-adjusted Mueller Hinton broth; CFU = colony forming units; MIC = minimum inhibitory concentration.

diverse PDFs was already described previously by Tobudic *et al.*, who investigated the influence of PDFs on the growth rates of *S. aureus*, *S. epidermidis*, *E. faecalis*, *P. aeruginosa*, and *C. albicans* (8). Likewise, several antibiotics were shown to have a reduced activity when evaluated *in vitro* in PDFs (5–7,9). The results of the present study suggest that the type of PDF used may have a relevant influence on the activity of the antibiotics investigated.

For the activity of cefepime and the carbapenem antibiotics ertapenem and meropenem, statistically significant differences were found in all PDFs evaluated compared with PDF control curves. A relevant reduction of bacteria, however, was observed only in Physioneal 40 at high concentrations (30 × MIC for carbapenems and ≥ 4 × MIC for cefepime) but not in the other PDFs investigated. This was rather surprising because carbapenems target the bacterial cell wall synthesis, and the time over MIC is their main pharmacokinetic/pharmacodynamics (PK/PD) parameter (10). As observed in the CA-MHB comparator solution, increasing drug concentrations of time-dependent antibiotics is generally not related to increasing activity. However, the observed bacteriostatic effect of PDFs might significantly hamper the antimicrobial activity of time-dependent antibiotics (11,12).

Figure 4 — Time-kill curves in CA-MHB and in 4 different peritoneal dialysis fluids at concentrations of meropenem equal to 1 x MIC, 4 x MIC, 8 x MIC and 30 x MIC. The dotted line shows the time of antibiotic addition, which was done directly before bacterial counts. The area in grey represents the time of dwell periods frequently used in clinical practice. CA-MHB = cation-adjusted Mueller Hinton broth; CFU = colony forming units; MIC = minimum inhibitory concentration.

In contrast, ciprofloxacin and tobramycin are concentration-dependent antimicrobial agents and are even active against non-proliferating bacteria (13,14). In line with this, tobramycin, followed by ciprofloxacin, were highly active against *E. coli* in all PDFs investigated. However, compared with the other PDFs and in contrast to the beta-lactams investigated, the activity of ciprofloxacin was markedly reduced in Physioneal 40 within the first 6 hours. The bactericidal activity of tobramycin, on the other hand, was significantly triggered when the amino acid-containing PDF Nutrineal PD4 was used. Thus, the specific composition of certain PDFs might impact the antimicrobial activity of antibiotics due to several factors related to drug-diluent interactions. Many antibiotics, including ciprofloxacin, ertapenem, and tobramycin, are known to be pH-dependent (15–18). Whereas Physioneal 40 has a physiological pH value of 7.4, the pH values of the other commercial PDFs investigated are lower, ranging from pH 5.0 to 6.6. Thus, the antimicrobial activity of pH-dependent antibiotics like ciprofloxacin and tobramycin might be reduced in clinical practice at the beginning of a PD dwell with a low-pH PDF. However, analysis of PDFs recovered from patients after 4- to 6-hour dwells revealed that a physiological pH is

Figure 5 — Time-kill curves in CA-MHB and in 4 different peritoneal dialysis fluids at concentrations of tobramycin equal to 1 x MIC, 4 x MIC, 8 x MIC and 30 x MIC. The dotted line shows the time of antibiotic addition, which was done directly before bacterial counts. The area in grey represents the time of dwell periods frequently used in clinical practice. CA-MHB = cation-adjusted Mueller Hinton broth; CFU = colony forming units; MIC = minimum inhibitory concentration.

reached during the IP dwell time, but no information exists about the velocity of this process (5,6). Therefore, in the present study, low-pH PDFs were adjusted to a pH of 7.30 – 7.50 at the beginning of each experiment in accordance with the literature (5,7).

Reduced drug stability in certain PDFs might further hamper antimicrobial activity. Unfortunately, for cefepime and ertapenem, no data on stability and biocompatibility with PDFs at body temperature are available, highlighting the need for further research in this area (3). Tobramycin, however, was shown to be stable at 37°C for at least 8 hours in glucose-containing PDFs, for 24 hours in icodextrin-containing PDFs, and for 4 hours in amino acid-containing PDFs (19–21). Ciprofloxacin was shown to be stable at body temperature for several weeks in a glucose-based PDF, but no stability data are available for icodextrin- or amino acid-containing PDFs (22). In addition, a very recent study compared the stability of meropenem in different commercial PDFs and revealed that meropenem is markedly more stable in Extraneal than in Physioneal 40 (unpublished data). Thus, at least for ciprofloxacin, tobramycin, and meropenem, drug stability in PDFs might not be the relevant factor for the reduced activity observed.

TABLE 1
Differences in log₁₀ CFU/mL Between Specific Peritoneal Dialysis Fluids With and Without Antibiotic Addition

Antibiotics	Mean difference of viable microorganisms compared with PDF control without antibiotics, log ₁₀ CFU/mL, (p value)				
	Dianeal PDG4 (6 hours)	Extraneal (6 hours)	Extraneal (10 hours)	Nutrineal PD4 (6 hours)	Physioneal 40 (6 hours)
Cefepime 0.06 µg/mL (= 1 × MIC)	-0.01 (p>0.05)	0.29 (p<0.01)	0.54 (p<0.001)	0.39 (p<0.05)	0.57 (p<0.05)
Cefepime 1.8 µg/mL (= 30 × MIC)	0.20 (p>0.05)	0.39 (p<0.001)	0.60 (p<0.001)	0.46 (p<0.01)	0.60 (p<0.05)
Ciprofloxacin 0.008 µg/mL (= 1 × MIC)	0.53 (p<0.05)	1.37 (p<0.001)	1.45 (p<0.001)	0.18 (p>0.05)	0.67 (p>0.05)
Ciprofloxacin 0.24 µg/mL (= 30 × MIC)	2.87 (p<0.01)	3.78 (p<0.001)	4.06 (p<0.001)	2.81 (p<0.001)	1.22 (p<0.05)
Ertapenem 0.008 µg/mL (= 1 × MIC)	0.50 (p<0.001)	0.77 (p<0.001)	0.72 (p<0.001)	0.34 (p<0.001)	-0.01 (p>0.05)
Ertapenem 0.24 µg/mL (= 30 × MIC)	0.74 (p<0.001)	1.18 (p<0.001)	0.88 (p<0.001)	0.47 (p<0.001)	0.66 (p>0.05)
Meropenem 0.03 µg/mL (= 1 × MIC)	0.13 (p>0.05)	0.26 (p>0.05)	0.33 (p<0.001)	0.28 (p<0.05)	0.21 (p>0.05)
Meropenem 0.9 µg/mL (= 30 × MIC)	0.54 (p<0.01)	0.67 (p<0.001)	0.94 (p<0.001)	0.45 (p<0.001)	0.56 (p<0.01)
Tobramycin 0.5 µg/mL (= 1 × MIC)	1.85 (p<0.001)	1.35 (p<0.001)	2.46 (p<0.001)	3.62 (p<0.001)	1.22 (p<0.001)
Tobramycin 15 µg/mL (= 30 × MIC)	3.53 (p<0.001)	3.59 (p<0.001)	3.51 (p<0.001)	4.40 (p<0.001)	3.54 (p<0.001)

CFU = colony forming units; PDF = peritoneal dialysis fluid; MIC = minimum inhibitory concentration.

Two different concentrations of cefepime, ciprofloxacin, ertapenem, meropenem, or tobramycin at clinical relevant time points (10 hours of incubation for icodextrin-based Extraneal, 6 hours of incubation for Dianeal PDG4, Extraneal, Nutrineal PD4, and Physioneal 40, all Baxter Healthcare Corp., Deerfield, IL, USA).

It should be mentioned that the present *in vitro* study is a static model without simulation of drug elimination or degradation over time, whereas IP drug concentrations in the clinical setting might vary over time. In the present study, drug concentrations were used in relation to the MIC of the bacterial strain used. The highest final drug concentrations (30 × MIC) applied were 1.8 µg/mL for cefepime, 0.24 µg/mL for ciprofloxacin, 0.24 µg/mL for ertapenem, 0.9 µg/mL for meropenem, and 15 µg/mL for tobramycin. All concentrations applied are thus easily achievable in the clinical setting when dosing regimens according to current guidelines are used

(3,23–26). However, despite longstanding clinical experience and a vast number of clinical trials and case series on the management of PDRP, recent systematic reviews and meta-analyses suggest that there is no superior antimicrobial agent to treat PDRP (27–30). Taking quinolones applied as monotherapy as an example, the reported efficacy rates range from 10 to 94% (31). Also, data on aminoglycosides in the management of PDRP are divergent (27). In fact, many authors claim that it is a difficult endeavor to clinically verify a superior therapy due to the significant heterogeneity regarding patient selection, administration routes, definition of peritonitis, and resolution,

as well as the number of subjects investigated among studies comparing different treatment regimens of PDRP. Therefore, recommendations for antibiotic choice in PDRP are often still based primarily on the susceptibility of the main causative organism and local resistance profiles. The results of the present study highlight the unique factors of PDRP and that care should be taken when susceptibility patterns evaluated with standard microbiological tests are applied (3). The antimicrobial activity might be reduced or even nullified in certain PDFs compared with standard broths, which might be of critical importance also in the clinical setting. Most clinical trials evaluating antimicrobial treatment in PDRP do not report on the PDFs used when antibiotics are applied IP.

Based on the results of the present study, further conclusions might be drawn for clinical applicability. For the treatment of PDRP caused by *E. coli*, the use of concentration-dependent antibiotics might be superior than time-dependent antimicrobial agents. Comparable results were recently published also for the gram-positive bacterium *Enterococcus faecalis*, where the concentration-dependent antibiotic daptomycin was superior to the time-dependent antibiotics ampicillin and linezolid (9). Further, comparing the 2 glucose-based PDFs, antimicrobial activity of ciprofloxacin is significantly delayed in Physioneal 40 but not in Dianeal PDG4.

The present findings support the increasing empirical use of aminoglycosides for short-term therapy, which appears to be safe and inexpensive, providing good gram-negative coverage. In addition, ciprofloxacin should be taken into account for empirical therapy if supported by local resistance patterns or as targeted therapy if continuous application can be provided.

In conclusion, the antimicrobial activity of cefepime, ertapenem, and meropenem is limited or nullified in certain PDFs *in vitro*, whereas ciprofloxacin and tobramycin show excellent activity. The choice of PDFs can impact the activity of antimicrobial agents and might further influence microbiological outcome. This should be taken into consideration when antibiotics are applied IP.

ACKNOWLEDGMENTS

This work was supported by the Institute of Nephrology and Hematooncology of the Karl Landsteiner Society. The authors thank Heidelinde Schranz from the Department of Internal Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, for valuable suggestions, excellent technical assistance and support in the microbiological work up.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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