

## PERITONITIS IN AUTOMATED PERITONEAL DIALYSIS: ANTIBIOTIC THERAPY AND PHARMACOKINETICS

Jose A. Diaz–Buxo,<sup>1</sup> Terri L. Crawford,<sup>1</sup> George R. Bailie<sup>2,3</sup>

*Fresenius Medical Care North America,<sup>1</sup> Lexington, Maryland; Albany College of Pharmacy,<sup>2</sup> Albany, New York; and Nephrology Pharmacy Associates,<sup>3</sup> Ann Arbor, Michigan, U.S.A.*

The use of automated peritoneal dialysis (APD) has increased markedly during the past decade, in response to the need to obtain higher clearances and to accommodate individual lifestyles. Peritonitis rates have been observed to be generally lower in APD as compared with continuous ambulatory peritoneal dialysis (CAPD). Still, peritonitis remains a significant complication of APD.

Many questions have been raised regarding the appropriateness of applying, to APD, the therapeutic antibiotic regimens used for treatment of peritonitis in CAPD. The original recommendations for treatment of peritonitis in PD mostly used peritoneal dialysate trough levels based on 2-L CAPD exchanges lasting 4 – 8 hours. Because APD uses shorter, more frequent exchanges, with variable fill volumes, at night, the clearance of many antibiotics is expected to be higher than in CAPD.

The use of single daily doses injected intraperitoneally (IP) during the long exchange of CAPD or APD has simplified the administration of antibiotics, and arguably, allows a uniform dose to be used for both modalities. However, the higher clearance of some antibiotics during rapid cycling may reduce tissue concentrations below the therapeutic range.

Recent pharmacokinetic studies have shed light on this important subject. Those studies should be used as a base from which to design more effective therapeutic guidelines.

### INCIDENCE OF PERITONITIS IN APD AND CAPD

The various theoretical reasons for differences in the incidence of peritonitis in CAPD and APD have been reviewed elsewhere (1). They are summarized

**KEY WORDS:** Peritonitis; automated peritoneal dialysis; pharmacokinetics.

Correspondence to: J.A. Diaz–Buxo, 1051 E. Morehead Street, Suite 250, Charlotte, North Carolina 28204 U.S.A.  
jose.diaz-buxo@fmc-na.com

in Table 1. Some of the considerations are strongly supported by solid *in vitro* and clinical observations; others seem to make logical sense, but have not been validated (2–4). To date, the strongest evidence supports the prolonged exchange-free periods of APD as an important factor in improving host defenses and reducing peritonitis.

A potential factor in the reduction of peritonitis that has received surprisingly little attention is adequacy. Nutrition strongly correlates with adequacy of dialysis. Nutrition is also instrumental in maintaining a healthy immune system, which is a requirement for fighting peritonitis. Thus, one could expect an association between peritonitis rates and dialysis dose.

The work of Locatelli *et al* (5), comparing two cohorts of patients on CAPD and APD, supports this notion. The peritonitis rates were 1.44 episodes per year and 0.63 episodes per year ( $p < 0.05$ ) for the CAPD and APD groups respectively. The mean weekly Kt/V values for the two groups were  $1.3 \pm 0.3$  and  $1.83 \pm 0.48$  ( $p < 0.001$ ) respectively. On the other hand, Mooraki *et al* (6) reported the highest peritonitis rates among patients with the highest Kt/V, but those authors were unable to find significant differences in hospital rates, erythropoietin doses, or serum albumin concentrations between patients with the lowest ( $\leq 1.4$ ) and the highest ( $\geq 1.9$ ) Kt/V. The potential association between dialysis dose and peritonitis rate deserves further study.

TABLE 1

Potential Reasons for Lower Incidence of Peritonitis  
in Automated Peritoneal Dialysis

Fewer connections
Better environmental control
Flush-before-fill fluid dynamics
Long dwell:
Higher dialysate cell counts
Higher proportion of mature monocytes
Better opsonin and cytokine response

Table 2 summarizes the peritonitis rates among CAPD and APD patients in various series. Peritonitis rates for CAPD have dropped markedly during the last decade with the use of the new disconnect systems. Rates for APD have remained relatively stable. Nonetheless, the vast majority of investigators are still reporting lower peritonitis rates for APD than for CAPD.

#### PHARMACOKINETIC STUDIES FOR SELECTED ANTIBIOTICS

Since 1987, the International Society for Peritoneal Dialysis (ISPD) has periodically provided updated recommendations for the treatment of PD-related infections (21). It was in 1996 that the guidelines first suggested combining a first-generation cephalosporin with an aminoglycoside for empiric therapy. This suggestion was put forward in an effort to reduce the use of vancomycin and thereby lessen the risk for the development of vancomycin resistance. Further, the 1996 recommendations promoted the use of intermittent as opposed to continuous IP antibiotic management.

Successful intermittent IP therapy requires adequate antibiotic penetration from the dialysate into the systemic circulation during the antibiotic-containing dwell. During subsequent antibiotic-free exchanges, the concentration gradient between the blood and the dialysate compartments provides the impetus for the maintenance of appropriate dialysate concentrations. Figure 1 demonstrates the differences between the serum and dialysate concentrations of a hypothetical antibiotic after continuous and intermittent IP administration.

The ISPD recommendations were most recently updated in 2000 (21). They now include dosing recommendations for patients treated with APD. Significantly, the empiric therapy recommendations have further changed: they now suggest combining a first-generation and third-generation cephalosporin, particularly for patients who retain some significant degree of residual renal function (RRF). That move was prompted by data demonstrating that courses of aminoglycosides could increase the rate at which RRF declines in PD patients (22).

The pharmacokinetics of intermittent regimens of cephalosporins, penicillins, vancomycin, and aminoglycosides have been well studied for CAPD, but data have only recently become available for APD. A brief review of recent studies of antibiotics in APD follows.

**Piperacillin:** Eight uninfected APD patient volunteers (5 being women) received a single intravenous (IV) dose (35 mg/kg actual body weight) of piperacillin (23). Blood and dialysate samples were collected at the beginning, middle, and end of dwells 1–3 (on the cycler) and at the end of dwells 4 and 5 (off the cycler) for a 24-hour period. Baseline and 24-hour urine samples were also collected from the 7 non anuric patients. Pharmacokinetic parameters were calculated assuming a one-compartment model. Glomerular filtration rate (GFR) and piperacillin clearances were normalized to a body surface area of 1.73 m<sup>2</sup>.

Mean dwell times were 2.25 hours and 7.26 hours on cycler and off cycler respectively. No statistical difference was seen in piperacillin half-life on or off cycler (2 hours vs 4.4 hours, respectively). Piperacillin total clearance was 31.3 ± 6 mL/min. Renal clearance and PD clearance accounted for 8.8% and 16.8% of

TABLE 2  
Peritonitis Rates (Episodes per Year) Among Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD) Patients

Reference	Standard CAPD	Disconnect CAPD	APD
Price and Suki, 1981 (7)	1.67	—	0.66
Walls <i>et al</i> , 1981 (8)	1.71	—	0.60
Diaz-Buxo <i>et al</i> , 1986 (9)	0.71	—	0.60
Rottembourg <i>et al</i> , 1988 (10)	1.03	0.52	0.50
Holley <i>et al</i> , 1990 (11)	1.30	0.50	0.30
Levy <i>et al</i> , 1990 (12)	1.48	—	0.93
de Fijter <i>et al</i> , 1991 (13)	—	1.20	0.60
Gahrmani <i>et al</i> , 1995 (14)	—	0.52	0.83
Vigilino <i>et al</i> , 1995 (15)	—	0.32	0.30
Diaz-Buxo, 1998 (16)	—	0.60	0.46
Troidle <i>et al</i> , 1998 (17)	—	1.15	1.20
Locatelli <i>et al</i> , 1999 (5)	—	1.44	0.63
Rodríguez-Carmona <i>et al</i> , 1999 (18)	—	0.64	0.31
Perez-Fontán <i>et al</i> , 1999 (19)	—	0.75	0.34
Huang <i>et al</i> , 2001 (20)	—	0.28	0.15

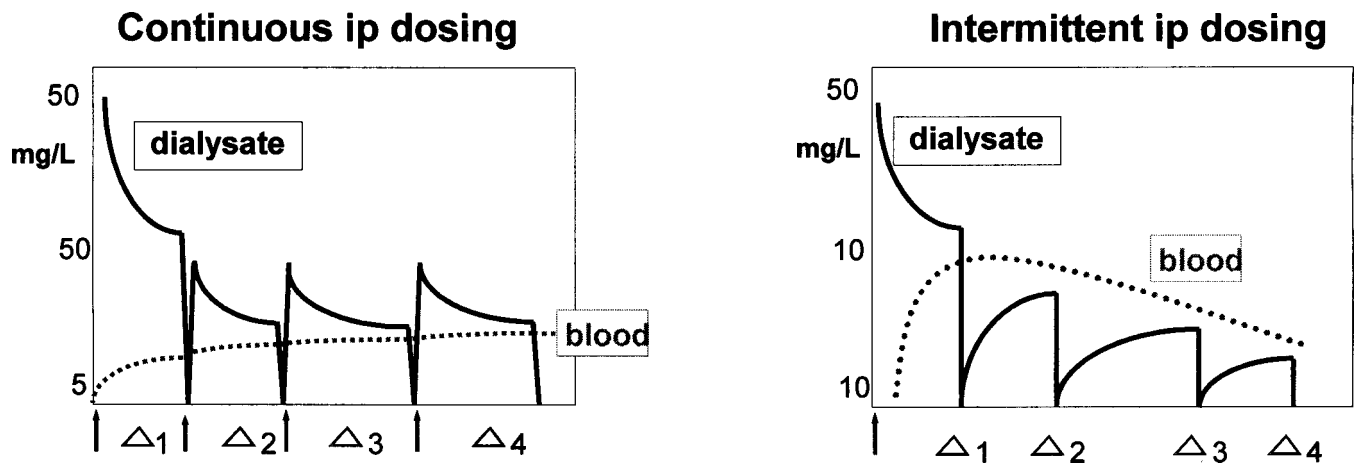


Figure 1 — Left panel: Modelled serum and dialysate concentrations following a continuous intraperitoneal (IP) regimen for an antibiotic. After a single loading dose of 1 g into the first exchange ( $\Delta_1$ ), each of the three subsequent 2-L exchanges ( $\Delta_2 - \Delta_4$ ) contains 100 mg of the antibiotic. Right panel: Modelled serum and dialysate concentrations following a single IP dose of 1 g antibiotic into the first exchange ( $\Delta_1$ ). Each of the three subsequent exchanges ( $\Delta_2 - \Delta_4$ ) are antibiotic-free.

total clearance. Renal clearance correlated well with GFR (renal clearance =  $0.86 \text{ GFR} + 0.1$ ,  $p < 0.00003$ ). Mean serum and end-of-dwell piperacillin concentrations were above the minimum inhibitory concentration (MIC:  $8 \mu\text{g/mL}$ ) for three cycler exchanges only. The authors calculated that the IV dosing requirements for piperacillin would be the same as the current recommendations for CAPD—that is, 4 g IV every 12 hours (Table 3).

**Cefazolin and Tobramycin:** Ten uninfected APD patients received a single IV dose of cefazolin (15 mg/kg) and tobramycin (0.6 mg/kg) (24). The methodology and pharmacokinetic determinations were essentially the same as described for the piperacillin study discussed earlier. The authors ad-

ministered the antibiotics by the IV route to simplify the study design. Cefazolin and tobramycin half-lives varied significantly on cycler and off cycler (cefazolin:  $10.67 \pm 4.66$  hours on cycler and  $23.09 \pm 5.6$  hours off cycler,  $p = 0.001$ ; tobramycin:  $14.27 \pm 4.53$  hours on cycler and  $68.5 \pm 26.47$  hours off cycler,  $p < 0.001$ ). With IV administration, the mean serum and dialysate concentrations for both antibiotics were above the MIC of susceptible organisms throughout a 24-hour period.

A model was developed to examine serum and dialysate concentrations after intermittent IP administration of cefazolin 15 mg/kg and tobramycin 0.6 mg/kg. The model predicted that IP cefazolin would provide adequate serum and dialysate concentrations for 24 hours. However, intermittent IP doses of tobramycin would need to be increased to 1.5 mg/kg for one exchange during the first day and then given as 0.5 mg/kg each subsequent day. The authors concluded that the current empiric dosing recommendations for CAPD-related peritonitis might be adequate for cefazolin (15 mg/kg). However, in APD patients, tobramycin doses need to be changed to 1.5 mg/kg IP on day 1, and to 0.5 mg/kg IP thereafter (Table 3).

**Vancomycin:** Using a study design similar to those already mentioned, the pharmacokinetics of vancomycin were studied in 10 APD patients (6 being women), who received a single IV dose (15 mg/kg total body weight) of vancomycin (25). Dwell times were  $2.3 \pm 0.1$  hours on cycler and  $7.3 \pm 0.1$  hours off cycler. The half-life of vancomycin was significantly different on cycler ( $11.6 \pm 5.2$  hours) and off cycler: ( $62.8 \pm 33.0$  hours,  $p < 0.001$ ). Vancomycin total clearance was  $7.4 \pm 2.0$  mL/min. Renal clearance and PD clearance accounted for 23.6% and 28.0% respectively of total clearance. Renal clearance correlated with

TABLE 3

Dosing of Antibiotics, by Intraperitoneal (IP) Intermittent Route,<sup>a</sup> in Automated Peritoneal Dialysis [Modified from (21)]

Drug	Schedule
Piperacillin	4000 mg IV, twice daily
Cefazolin	20 mg/kg daily, in first or second ambulatory dwell
Tobramycin	Loading dose (day 1) 1.5 mg/kg Maintenance dose 0.5 mg/kg daily, in first or second ambulatory dwell
Vancomycin	Loading dose 35 mg/kg Maintenance dose 15 mg/kg IP daily (Use caution: See text.)
Fluconazole	200 mg IP, every 24–48 h

IV =intravenous.

<sup>a</sup> Unless otherwise specified, IP doses are added to the first ambulatory dwell after the automated exchanges.

GFR (renal clearance = 0.90 GFR - 1.01,  $r^2 = 0.79$ ,  $p = 0.008$ ). Mean serum and end-of-dwell dialysate concentrations of vancomycin were above the MIC of susceptible organisms (5 µg/mL) only for the first cyclical exchange and second ambulatory exchange.

The results of the study suggested that, to provide adequate concentrations for susceptible organisms over a 24-hour period, current intermittent vancomycin dosing recommendations for APD-related peritonitis would need to be changed to 35 mg/kg IP on day 1, and 15 mg/kg IP thereafter (for example, once daily). However, it should be noted that, to obtain adequate dialysate levels, the serum concentrations would have to be maintained at very high levels for a sustained period of time. These high levels could potentially lead to toxicity (Figure 2). The authors therefore recommended against vancomycin dosing in APD, unless the cycle time is kept relatively uniform. Alternatively, the patients could be temporarily converted to CAPD. The pharmacokinetics of vancomycin in APD patients prescribed more than 3 cyclical exchanges warrants further investigation.

Table 3 presents an overview of the APD dosing recommendations based on the aforementioned studies and other recent literature. Appropriate dosing of antibiotics in APD could both improve the success of the therapy and prevent the adverse effects associated with excessive doses. Further pharmacokinetic analyses are needed with emphasis on antibiotics not yet studied.

**REFERENCES**

1. Diaz-Buxo JA, Crawford T. Peritonitis and antibiotic therapy in patients on cyclical peritoneal dialysis—an update. *Adv Perit Dial* 2000; 16:229–32.
2. Verger C, Luzar MA. *In vitro* study of CAPD Y-line system. *Adv CAPD* 1986; 2:160–4.
3. de Fijter CWH, Verbrugh HA, Oe PL, Peters EDJ, van der Meulen J, Donker AJM, *et al.* Peritoneal defenses in continuous ambulatory versus continuous cyclic peritoneal dialysis. *Kidney Int* 1992; 42:947–50.
4. Wrenger E, Baumann C, Behrend M, Zamore E, Schindler R, Brunkhorst R. Peritoneal mononuclear cell differentiation and cytokine production in intermittent and continuous automated peritoneal dialysis. *Am J Kidney Dis* 1998; 31:234–41.
5. Locatelli A, Marcos G, Gomez M, Alvarez S, DeBenedetti L. Comparing peritonitis in continuous ambulatory peritoneal dialysis patients versus automated peritoneal dialysis patients. *Adv Perit Dial* 1999; 15:193–6.
6. Mooraki A, Kliger A, Gorban-Brennan NL, Juergensen P, Brown E, Finkelstein FO. Weekly Kt/V urea and selected outcome criteria in 56 randomly selected CAPD patients. *Adv Perit Dial* 1993; 9:92–6.
7. Price C, Suki W. New modifications of peritoneal dialysis: options in the treatment of patients with renal failure. *Am J Nephrol* 1981; 1:97–104.
8. Walls J, Smith BA, Feehally J, Tavernel D, Turgan C. CCPD—an improvement on CAPD. In: Gahl GM, Keisel M, Nolph KDA, eds. *Advances in Peritoneal Dialysis*.

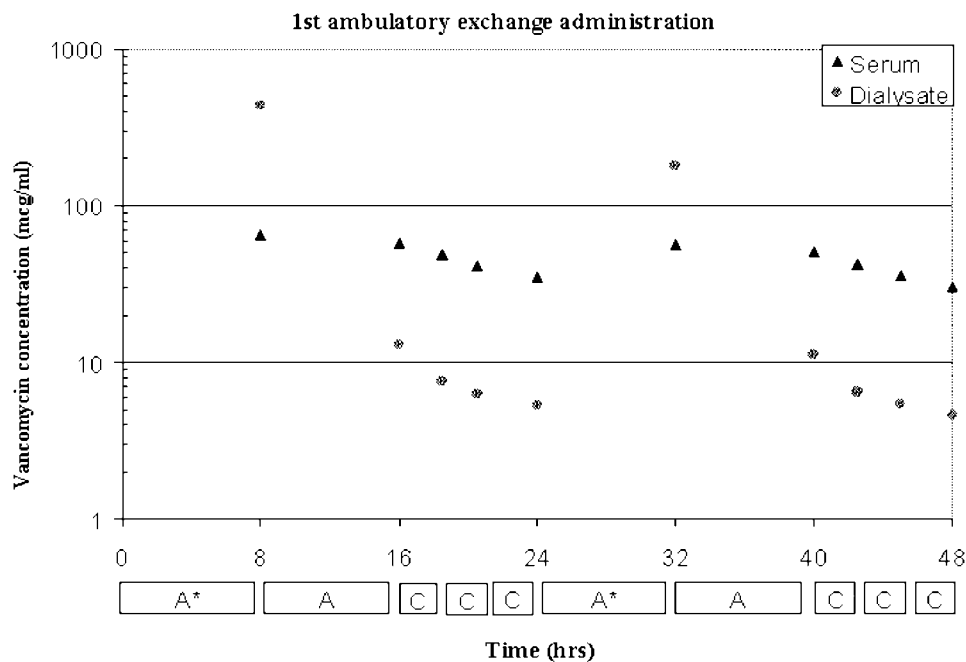


Figure 2 — Modelled vancomycin serum and dialysate concentrations at end of dwells over a 48-hour period if administered to a 70-kg individual. In this model, vancomycin 2500 mg (35 mg/kg) was administered intraperitoneally (IP) into the first ambulatory dwell (A\*) of day 1, and 1000 mg (15 mg/kg) was administered IP into the first ambulatory dwell (A\*) of day 2. Each of the other ambulatory dwells (A) and cyclical dwells (C) were antibiotic-free. Note that serum concentrations of vancomycin are sustained in the 30 – 60 mg/L range using this regimen. [From (25), reprinted with permission]

DIAZ-BUXO *et al.*

PERITONITIS IN APD: PHARMACOKINETICS

- Amsterdam: Excerpta Medica; 1981: 141-3.
9. Diaz-Buxo JA, Walker PJ, Burgess WP, Chandler JT, Farmer CD, Holt KL. Current status of CCPD in the prevention of peritonitis. *Adv CAPD* 1986; 2:145-8.
  10. Rottembourg J, Brouard R, Issad B, Allouache M, Nguyen J, Montassine MC, *et al.* Prevention of peritonitis during continuous ambulatory peritoneal dialysis. Value of disconnectable systems (French). *Presse Med* 1988; 17:1349-53.
  11. Holley JL, Bernardini J, Piraino B. Continuous cycling peritoneal dialysis is associated with lower rates of catheter infections than continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1990; 16:133-6.
  12. Levy M, Balfe JW, Geary D, Fryer-Keene SP. Factors predisposing and contributing to peritonitis during chronic peritoneal dialysis in children: a ten-year experience. *Perit Dial Int* 1990; 10:263-9.
  13. de Fijter CWH, Oe PL, Nauta JJP, van der Meulen J, ter Wee PM, Snoek FJ, *et al.* A prospective, randomized study comparing the peritonitis incidence of CAPD and Y-connector (CAPD-Y) with continuous cyclic peritoneal dialysis (CCPD). *Adv Perit Dial* 1991; 7:186-9.
  14. Gahrmani N, Gorban-Brennan N, Kliger AS, Finkelstein FO. Infection rates in end-stage renal disease patients treated with CCPD and CAPD using the UltraBag system. *Adv Perit Dial* 1995; 11:164-6.
  15. Viglino G, Gandolfo C, Virga G, Cavalli PL. Role of automated peritoneal dialysis within a peritoneal dialysis program. *Adv Perit Dial* 1995; 11:134-8.
  16. Diaz-Buxo JA. Continuous ambulatory and continuous cycling peritoneal dialysis. In: LaGreca G, Chiaromonte S, Fabris A, Feriani M, Ronco C, eds. Peritoneal dialysis. Milan: Wichtig Editore; 1986: 257-64.
  17. Troidle L, Gorban-Brennan N, Kliger AS, Finkelstein FO. Continuous cycler therapy, manual peritoneal dialysis therapy, and peritonitis. *Adv Perit Dial* 1998; 14:137-41.
  18. Rodríguez-Carmona A, Fontán MP, Falcón TG, Rivera CF, Valdés F. A comparative analysis on the incidence of peritonitis and exit-site infection in CAPD and automated peritoneal dialysis. *Perit Dial Int* 1999; 19: 253-8.
  19. Perez-Fontán M, Rodríguez-Carmona A, García-Falcón T, Fernández-Rivera C, Valdés F. Incidence of peritonitis (P) and exit site infection (ESI) in CAPD and automated PD (APD). A comparative study (Abstract). *Perit Dial Int* 1999; 19(Suppl 1):S35.
  20. Huang JW, Hung KY, Yen CJ, Wu KDA, Tsai TJ. Comparison of infectious complications in peritoneal dialysis patients using either a twin-bag system or automated peritoneal dialysis. *Nephrol Dial Transplant* 2001; 16:604-7.
  21. Keane WF, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, *et al.* ISPD guidelines/recommendations. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. *Perit Dial Int* 2000; 20:396-411.
  22. Shemin D, Maaz D, St. Pierre D, Kahn SI, Chazan JA. Effect of aminoglycoside use on residual renal function in peritoneal dialysis patients. *Am J Kidney Dis* 1999; 34:14-20.
  23. Manley HJ, Bailie GR, Frye R, McGoldrick MD. Intermittent intravenous piperacillin pharmacokinetics in automated peritoneal dialysis patients. *Perit Dial Int* 2000; 20:686-93.
  24. Manley HJ, Bailie GR, Frye R, Hess LD, McGoldrick MD. Pharmacokinetics of intermittent intravenous cefazolin and tobramycin in patients treated with automated peritoneal dialysis. *J Am Soc Nephrol* 2000; 11:1310-16.
  25. Manley HJ, Bailie GR, Frye RF, McGoldrick MD. Intravenous vancomycin pharmacokinetics in automated peritoneal dialysis patients. *Perit Dial Int* 2001; 21: 378-85.