Pharmacokinetic Principles of intraperitoneal antibiotics

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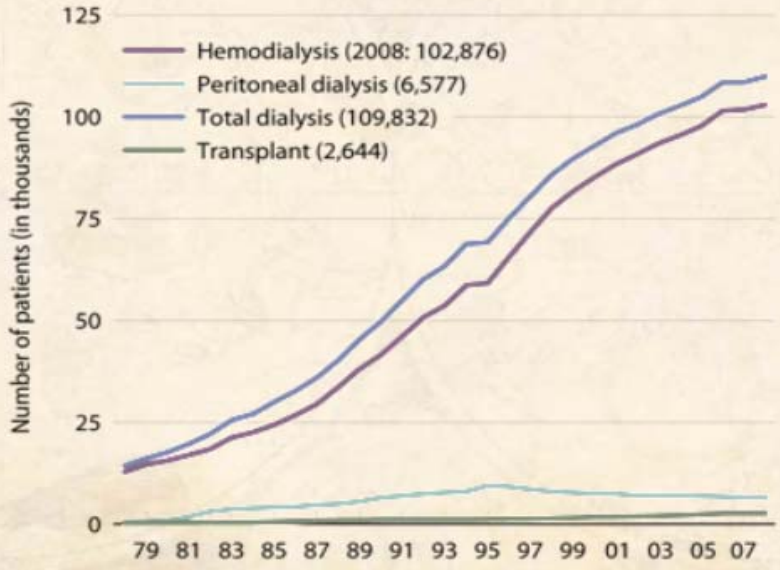
Objectives

- 1) Review pharmacokinetic principles of IP dosing
- 2) Consider important factors affecting the distribution to and clearance from peritoneum
- 3) Review pharmacokinetic studies of commonly used IP antibiotics in CAPD and APD
- 4) Dosing and monitoring of antibiotics in peritonitis

Incident patient counts (USRDS), by first modality

Figure 4.1 (Volume 2)



Incident ESRD patients; peritoneal dialysis counts include CAPD & CCPD only.

USRDS 2010 ADR

USRDS

Introduction

- Peritonitis remains the most serious complication and cause of change in treatment modality, morbidity & mortality
- Prompt and effective management of peritonitis crucial for preventing scarring of peritoneum and improved clinical outcomes
- Rate < 1/18 months (0.67/year at risk), some centers 1/41-52 months (0.29-0.23/year at risk)
- Latest update in ISPD guidelines on the management of peritonitis 2010, intermittent IP dosing recommended along with continuous IP dosing.

ISPD PERITONITIS MANAGEMENT : 2010 UPDATE

Patient Education

- Immediately report cloudy effluent, abdominal pain, and/or fever to PD unit
- Save drained cloudy dialysate and bring to clinic
- Treatment will be adding intraperitoneal antibiotics for up to 3 weeks
- Report worsening symptoms or persistent cloudiness to PD unit
- Schedule retraining for technique issues

Outcomes Evaluation

- Collect data to include
  - Date of culture, organism identified, drug therapy used
  - Date infection resolved
  - Recurrent organisms, date of drug therapy
  - Method of interim renal replacement therapy
  - Date of catheter removal
  - Date of new catheter reinsertion
  - Documentation of contributing factors
    - Break in technique, patient factors, exit-site infections, tunnel infections
  - Date of reeducation/training
- Enter data into catheter management database

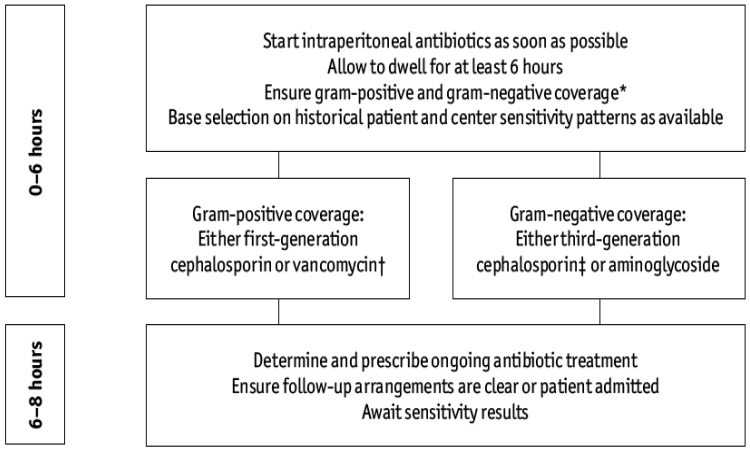


Figure 1 — Initial management of peritonitis: *Continued assessment and modification of therapy based on culture and sensitivity

ISPD 2010 GUIDELINES

TABLE 4
Intraperitoneal Antibiotic Dosing Recommendations for CAPD Patients[a]

	Intermittent (per exchange, once daily)	Continuous (mg/L; all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin, netilmicin, or tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin, cephalothin, or cephradine	15 mg/kg	LD 500, MD 125
Cefepime	1000 mg	LD 500, MD 125
Ceftazidime	1000–1500 mg	LD 500, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Penicillins		
Amoxicillin	ND	LD 250–500, MD 50
Ampicillin, oxacillin, or nafcillin	ND	MD 125
Azlocillin	ND	LD 500, MD 250
Penicillin G	ND	LD 50000 units, MD 25000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Aztreonam	ND	LD 1000, MD 250
Daptomycin (115)	ND	LD 100, MD 20
Linezolid (41)	Oral 200–300 mg q.d.	
Teicoplanin	15 mg/kg	LD 400, MD 20
Vancomycin	15–30 mg/kg every 5–7 days	LD 1000, MD 25
Antifungals		
Amphotericin	NA	1.5
Fluconazole	200 mg IP every 24–48 hours	
Combinations		
Ampicillin/sulbactam	2 g every 12 hours	LD 1000, MD 100
Imipenem/cilastin	1 g b.i.d.	LD 250, MD 50
Quinupristin/dalfopristin	25 mg/L in alternate bags[b]	
Trimethoprim/sulfamethoxazole	Oral 960 mg b.i.d.	

ND = no data; q.d. = every day; NA = not applicable; IP = intraperitoneal; b.i.d. = 2 times per day; LD = loading dose in mg/L; MD = maintenance dose in mg/L.

[a] For dosing of drugs with renal clearance in patients with residual renal function (defined as >100 mL/day urine output), dose should be empirically increased by 25%.

[b] Given in conjunction with 500 mg intravenous twice daily.

ISPD 2010 GUIDELINES

TABLE 5
Intermittent Dosing of Antibiotics in Automated Peritoneal Dialysis

Drug	IP dose
Cefazolin	20 mg/kg IP every day, in long day dwell (112)
Cefepime	1 g IP in 1 exchange per day
Fluconazole	200 mg IP in 1 exchange per day every 24–48 hours
Tobramycin	LD 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP each day in long dwell (112)
Vancomycin	LD 30 mg/kg IP in long dwell; repeat dosing 15 mg/kg IP in long dwell every 3–5 days (aim to keep serum trough levels above 15 µg/mL)

IP = intraperitoneal; LD = loading dose.

ADVANTAGES OF IP VS IV ANTIBIOTIC ADMINISTRATION

- Localized, immediate and supratherapeutic peritoneal concentrations (Total dose in a much smaller volume)
- Well absorbed route of administration ; increased absorption especially with an inflammed peritoneum with an adequate dwell time.
- Redistribution down a concentration gradient into the peritoneal cavity occurs once therapeutic concentrations are achieved in the vascular compartment
- Convenient intermittent (commonly once daily) administration for patient self administration
- Minimize risk of contamination with repeated administration
- No need for i/v or po access, convenient for patient administration, especially if nausea/vomiting present

CONTINUOUS IP DOSING VS INTERMITTENT IP DOSING

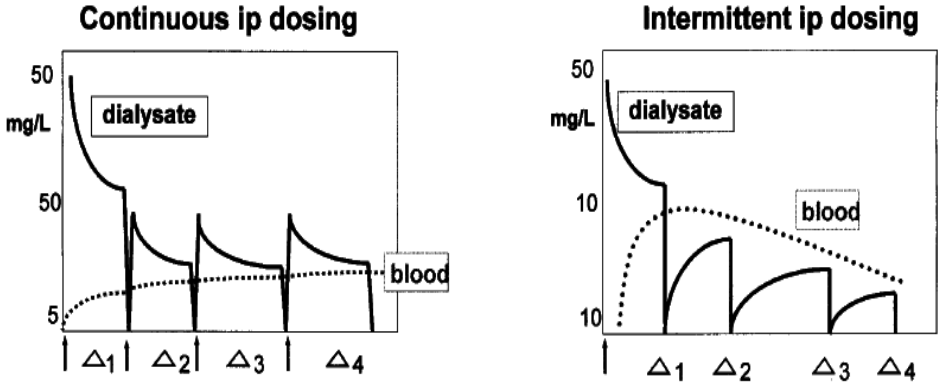
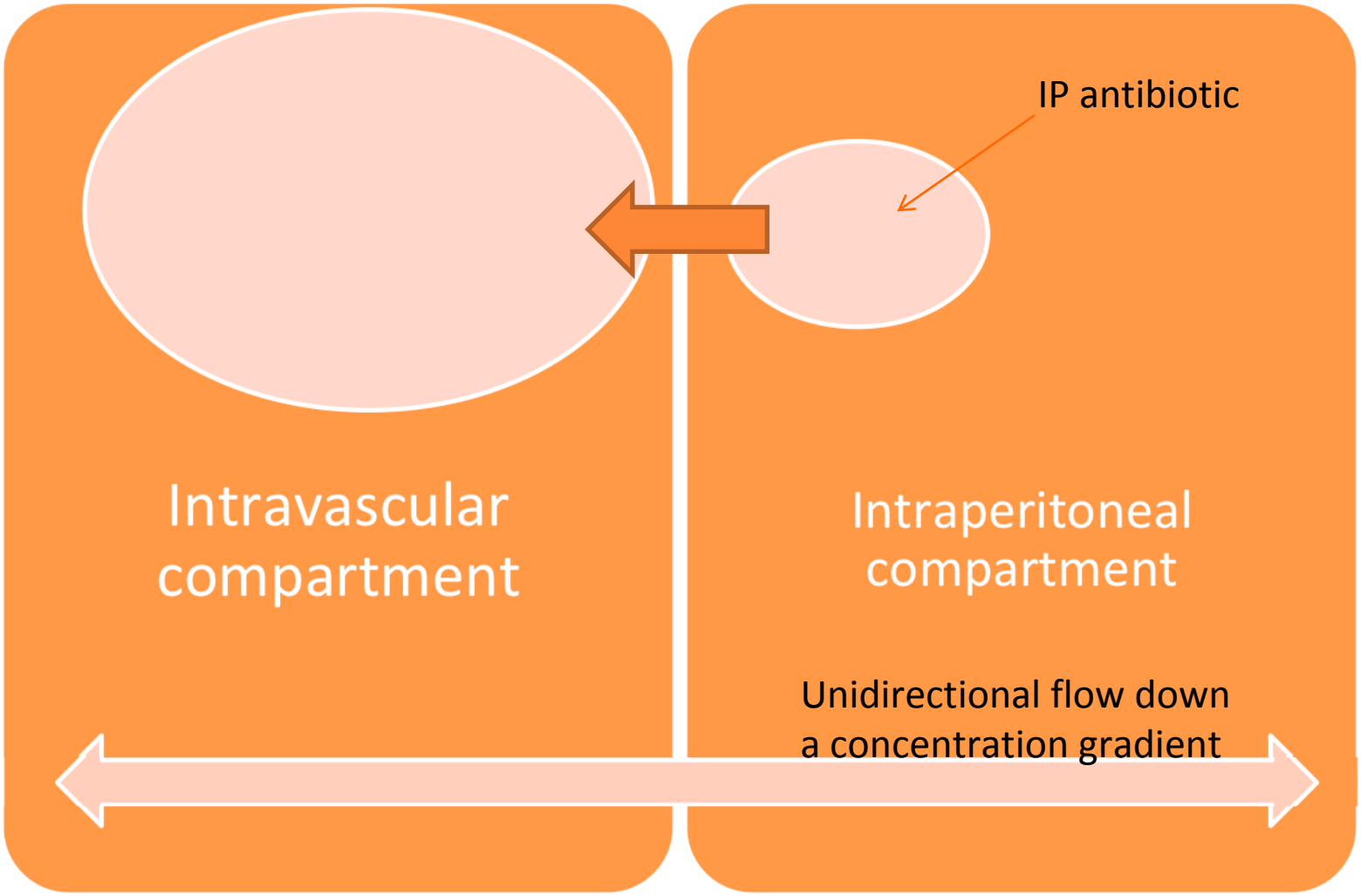
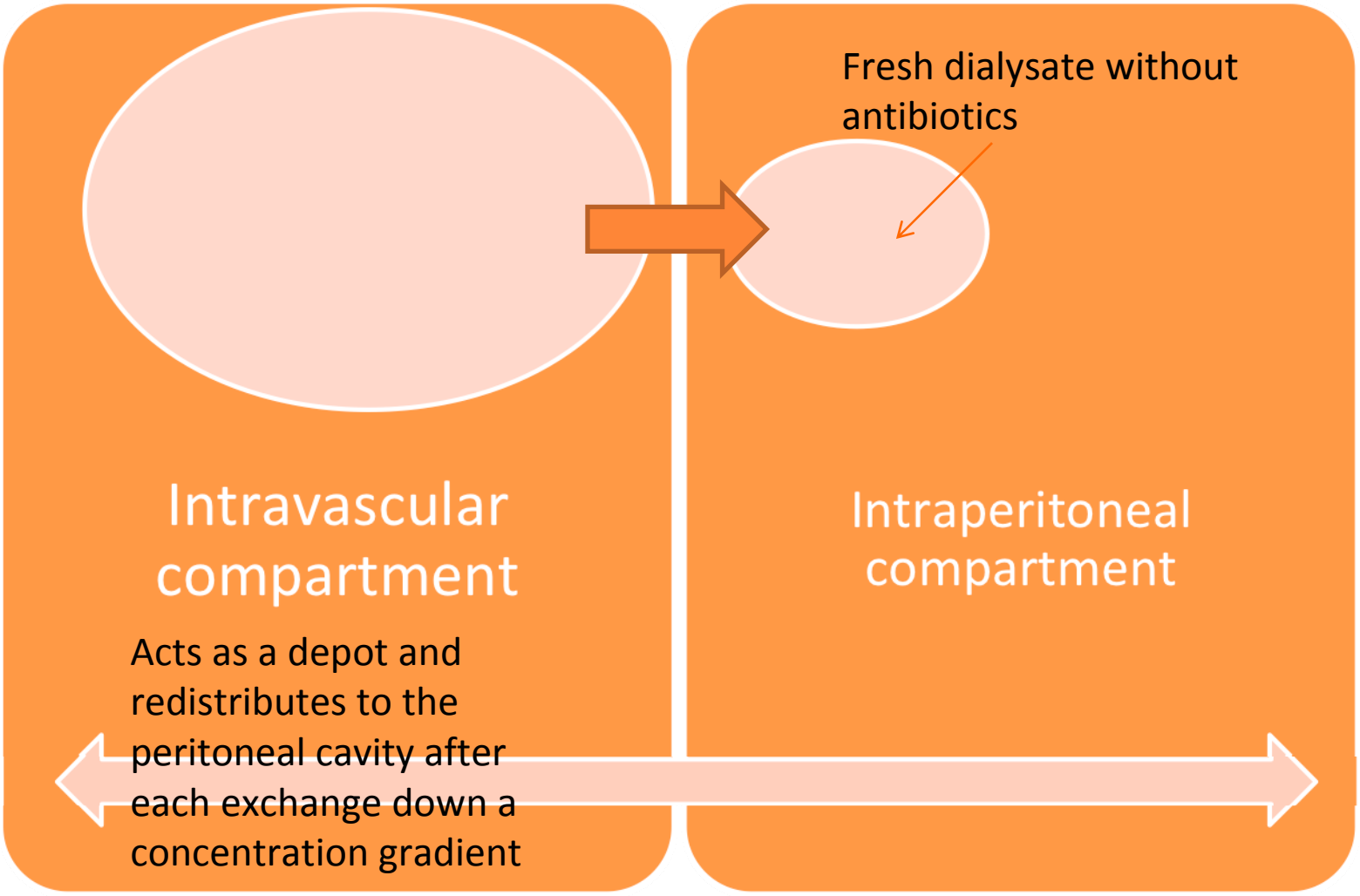


Figure 1 — Left panel: Modelled serum and dialysate concentrations following a continuous intraperitoneal (IP) regimen for an antibiotic. After a single loading dose of 1 g into the first exchange (Δ1), each of the three subsequent 2-L exchanges (Δ2 – Δ4) contains 100 mg of the antibiotic. Right panel: Modelled serum and dialysate concentrations following a single IP dose of 1 g antibiotic into the first exchange (Δ1). Each of the three subsequent exchanges (Δ2 – Δ4) are antibiotic-free.

INTRAPERITONEAL PHARMACOKINETICS



INTRAPERITONEAL PHARMACOKINETICS



FACTORS AFFECTING THE MOVEMENT OF DRUGS FROM EACH COMPARTMENT

- Size of molecules
- Degree of protein binding
- Volume of distribution of drug
- Dwell time –shorter in APD
- Concentration gradient
- Peritoneum inflammation
- Surface area
- Peritoneal blood flow
- Elimination routes

CAPD VS APD

- CAPD

  typical regimen 3 x 2L (4-6 h dwell) and an overnight 1 x 2 L (8-12 h dwell), total volume of dialysate about (8 to10 L)

- APD

  Automated overnight (3 or more exchanges) of 8-12L over 12 hours and usually one to two x 2L longer dwell (6 to 8 hours) in the day, total volume of 12-16 L

** variability of dialysis prescription

APD VS CAPD

- Greater volumes of dialysate used in APD (12-16 L vs 6-10 L of dialysate/day) for higher clearance
- APD accommodates lifestyles and convenience of dialysis exchanges
- Probably no difference in the rate of RRF loss
- Rate of peritonitis may be less than CAPD but magnitude of difference depends on local practices
- Technique success higher for APD but limited to the first year of therapy
- No significant difference, but APD may confer higher survival advantage in high transporters

PHARMACOKINETIC STUDIES OF IP ANTIBIOTICS

J Am Soc Nephrol 11: 1117–1121, 2000

Pharmacokinetics of Once Daily Intraperitoneal Cefazolin in Continuous Ambulatory Peritoneal Dialysis Patients

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PHARMACOKINETICS OF IP CEFAZOLIN

- 10 Stable, non-infected, volunteer, CAPD patients
- All pt received 1g (500mg/L) in the first dwell (2L 1.5 % D bag) for 6 h
- Blood and dialysate samples collected at 0, 0.5, 1, 2, 3, 6 (end of first dwell), 2 x 3h dwells and an overnight 12 h dwell.
- PK calculation assuming a monoexponential model, first order kinetics.

PK OF IP CEFAZOLIN

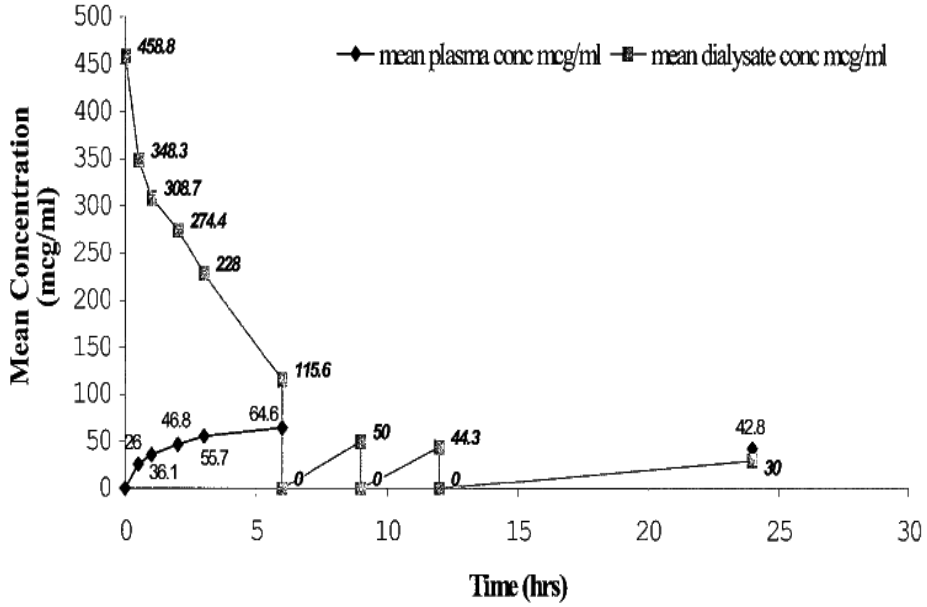

Figure 1. Concentration–time profile of plasma and dialysate after intraperitoneal administration of cefazolin.

CEFAZOLIN IN CAPD PK PARAMETERS

Table 1. Pharmacokinetic parameters[a]

Patient	F (%)	kpc-cc (h^{-1})	kel (h^{-1})	$t_{1/2pc}$ (h)	$t_{1/2el}$ (h)	$t_{1/2eq}$ (h)	V_d (L/kg)	CL_{total} (ml/min)	CL_r (ml/min)	CL_p (ml/min)	Weight (kg)	Transport Status
1	74.4	0.203		3.41							41.1	LA
2	70.4	0.126	0.016	5.49	44.42	4.89	0.18	2.17	0	2.17	46.0	HI
3	79.3	0.303	0.026	2.88	26.45	2.11	0.29	7.48	2.82	4.66	60.0	LA
4	79.7	0.286	0.016	2.42	44.03	2.29	0.26	3.95	1.11	2.84	57.2	HA
5	79.8	0.266	0.009	2.60	80.00	2.52	0.19	1.38	0	1.38	51.6	LA
6	80.0	0.256	0.009	2.71	78.94	2.62	0.16	1.75	0	1.75	75.4	HA
7	78.9	0.252	0.039	2.75	17.92	2.39	0.23	6.02	1.20	4.83	41.0	HA
8	78.1	0.289	0.025	2.40	27.94	2.21	0.23	5.08	2.62	2.45	54.2	HA
9	80.0	0.233	0.026	2.97	26.25	2.67	0.14	5.16	0.85	4.31	83.1	LA
10	78.0	0.267	0.053	2.59	13.09	2.16	0.13	7.06	0	7.06	64.0	LA
Mean	77.9	0.248	0.024	2.96	39.89	2.65	0.20	4.45	1.72	3.48	57.0	
SD	3.1	3.149	0.014	0.94	25.35	0.86	0.05	2.28	0.92	1.83	14.0	

[a] F, bioavailability; kpc-cc, rate constant for the removal of cefazolin from peritoneal cavity; kel, plasma elimination rate constant; $t_{1/2pc}$, elimination half-life of cefazolin in peritoneal cavity; $t_{1/2el}$, plasma elimination half-life; $t_{1/2eq}$, equilibration half-life; V_d, apparent volume of distribution of cefazolin; CL_{total}, CL_r, and CL_p, total body, renal, and peritoneal clearances, respectively; LA, low-average; HA, high-average; HI, high.

AQ1—Au: Units shown correctly?

PK RESULTS FOR IP CEFAZOLIN IN CAPD

- F of IP cefazolin, biovailability = 78% (70-80%) non-inflammed peritoneum
- Elimination Half-life = 40 h (80 to 13h)
- Equilibration half life = 2.65 +/- 0.86h
- PD half life (first dwell)= 3 +/- 0.94 h
- Vd = 0.2 +/- 0.05 L/kg

CONCLUSIONS

- A once daily IP dose of 1g cefazolin in 6 h dwell provided serum and dialysate concentrations that were above MIC over 24 h.
- All patients had creatinine clearance ranging between 0 and 7 ml/min.
- For pts with higher residual renal function Clcr >7 ml/min, higher or more frequent dosing may be required.

J Am Soc Nephrol 11: 1310–1316, 2000

Pharmacokinetics of Intermittent Intravenous Cefazolin and Tobramycin in Patients Treated with Automated Peritoneal Dialysis

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PK CEFAZOLIN AND TOBRAMYCIN IN APD PATIENTS

- Phase 1: 10 stable, non-infected, volunteer patients
- IV cefazolin 15mg/kg and IV 0.6mg/kg of tobramycin. Reverse order : Start with the dwell using cycler (3 exchanges x 2L over 8h) and continue off cycler of 2x 2L, 8h dwell each).
- Dialysate drained and retained at the end of each cycler dwell & at 24 hours
- Serum samples drawn at the midpoint and end of each dwell (on cycler) and at 24 hours.
- Phase 2
- Model prediction of IP dosing for serum and dialysate concentrations using PK parameters determined in Phase 1

RESULTS

Table 2. Mean cefazolin and tobramycin pharmacokinetic parameters on and off cycler[a]

Drug	k_{el} (h^{-1}) Dwell 1 to 3	$t½$ (h) Dwell 1 to 3	k_{el} (h^{-1}) Dwell 4 to 5	$t½$ (h) Dwell 4 to 5	k_{sd} (h^{-1}) Dwell 1 to 3	$t½$ k_{sd} (h) Dwell 1 to 3	V_d (L/kg)
Cefazolin							
mean	0.08	10.67	0.03	23.09	0.56	1.25	0.14
SD	0.03	4.66	0.01	5.60	0.03	0.07	0.03
Tobramycin							
mean	0.05	14.27	0.01	68.50	0.49	1.47	0.21
SD	0.01	4.53	0.00	26.47	0.10	0.28	0.06

[a] k_{el}, serum elimination rate; $t½$, half-life; k_{sd}, serum to dialysate transfer rate; V_d, volume of distribution.

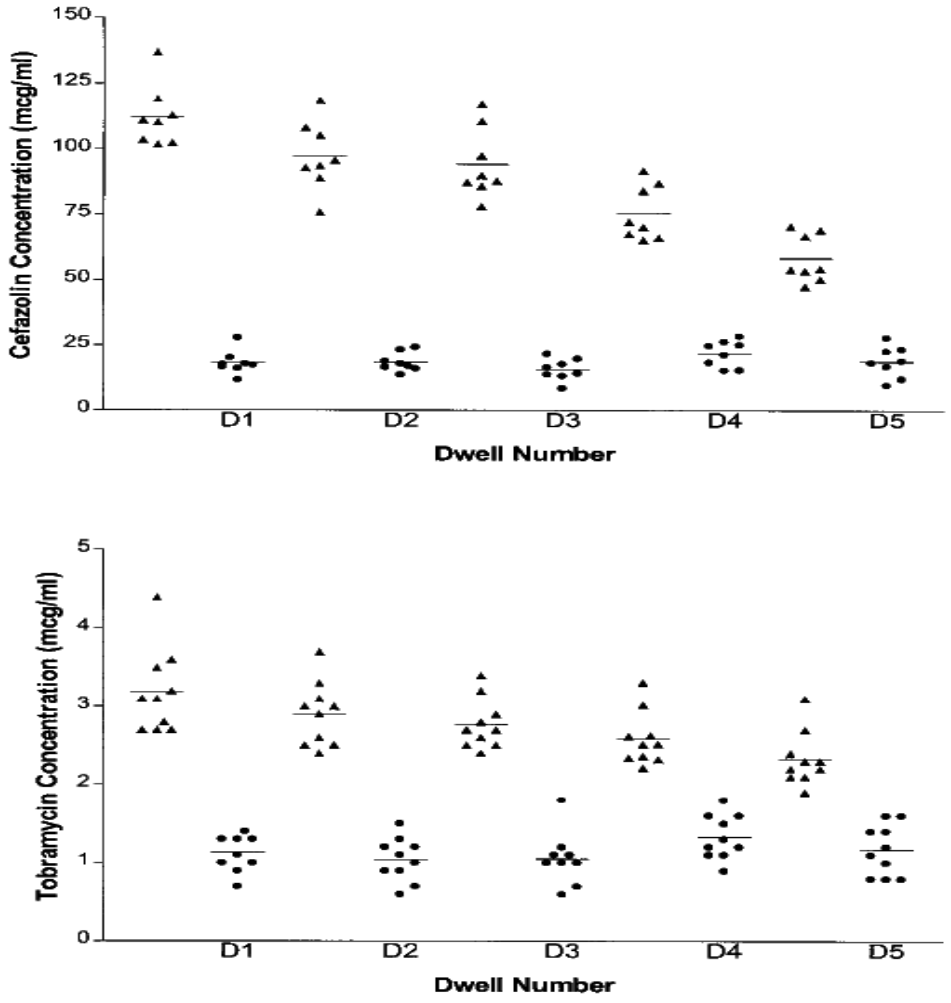

Figure 1. Mean cefazolin and tobramycin serum and dialysate concentrations at end of dwell. ●, dialysate concentration; ▲, serum concentration.

Table 3. Intraperitoneal cefazolin (15 mg/kg) and tobramycin (0.6 mg/kg) model-predicted serum and dialysate concentrations at end of dwell for first or second ambulatory exchange administration in a 70-kg individual

Dwell	Cefazolin (mcg/ml)		Tobramycin (mcg/ml)	
	Serum	Dialysate	Serum	Dialysate
1st ambulatory[a]	56.2	150.0	1.4	10.0
2nd ambulatory	43.9	13.6	1.3	0.7
Cycler 1	40.3	7.0	1.2	0.4
Cycler 2	37.0	6.4	1.1	0.4
Cycler 3	34.0	5.9	1.0	0.4
2nd ambulatory[a]	56.2	150.0	1.4	10.0
Cycler 1	51.6	8.9	1.3	0.5
Cycler 2	47.4	8.2	1.2	0.4
Cycler 3	43.5	7.5	1.1	0.4
1st ambulatory	34.0	10.5	1.0	0.5

[a] Antibiotics given.

CEFZOLIN DOSING IN APD

- Cefazolin 15mg/kg IV gave 24h serum and dialysate concentrations of 57.7 mcg/dl and 18.9 mcg/ml respectively, adequate for coverage (>8 mcg/ml) for even modestly resistant organisms.
- Model predictions indicate adequate dialysate and serum concentrations if cefazolin 15 mg/kg was instilled in the second ambulatory exchange. Higher dose of 20mg/kg IP q day would be needed if instilled in first ambulatory dwell.

TOBRAMYCIN DOSING IN APD

- Intermittent IP tobramycin yielded adequate dialysate concentrations for the antibiotic dwells only.
- Model-predicted tobramycin 1.43mg/kg IP in first long dwell or 1.35 mg/kg IP in second dwell, followed by 0.5mg/kg in subsequent daily IP administration would provide dialysate concentrations > 1.0 mcg/ml over 24-h period
- T1/2 41 hours, steady-state in 1 week, leading to accumulation

OTOTOXICITY OF AMINOGLYCOSIDES

- A study reported sstained serum concentrations of 4.4 to 4.9 mcg/ml of tobramycin over 9.5 days did not show ototoxicity
- Proposed PK dosing of tobramycin1.5mg/kg LD followed by 0.5 mg/kg daily IP dosing would give serum concentration of 2.4 to 3.5 mcg/ml at steady state
- Prolonged treatment >2 weeks or repeated treatments will increase risk of toxicity.

DECLINE OF USE OF AMINOGLYCOSIDES

- Less use of aminoglycosides because of concern for nephro and ototoxicities
- May increase the rate of residual renal function decline
- RRF is highly correlated to mortality in PD patients

Peritoneal Dialysis International, Vol. 19, pp. 65–70
Printed in Canada.

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PHARMACOKINETICS OF INTERMITTENT INTRAPERITONEAL CEFAZOLIN IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS

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PDI JANUARY 1999 – VOL. 19, NO. 1

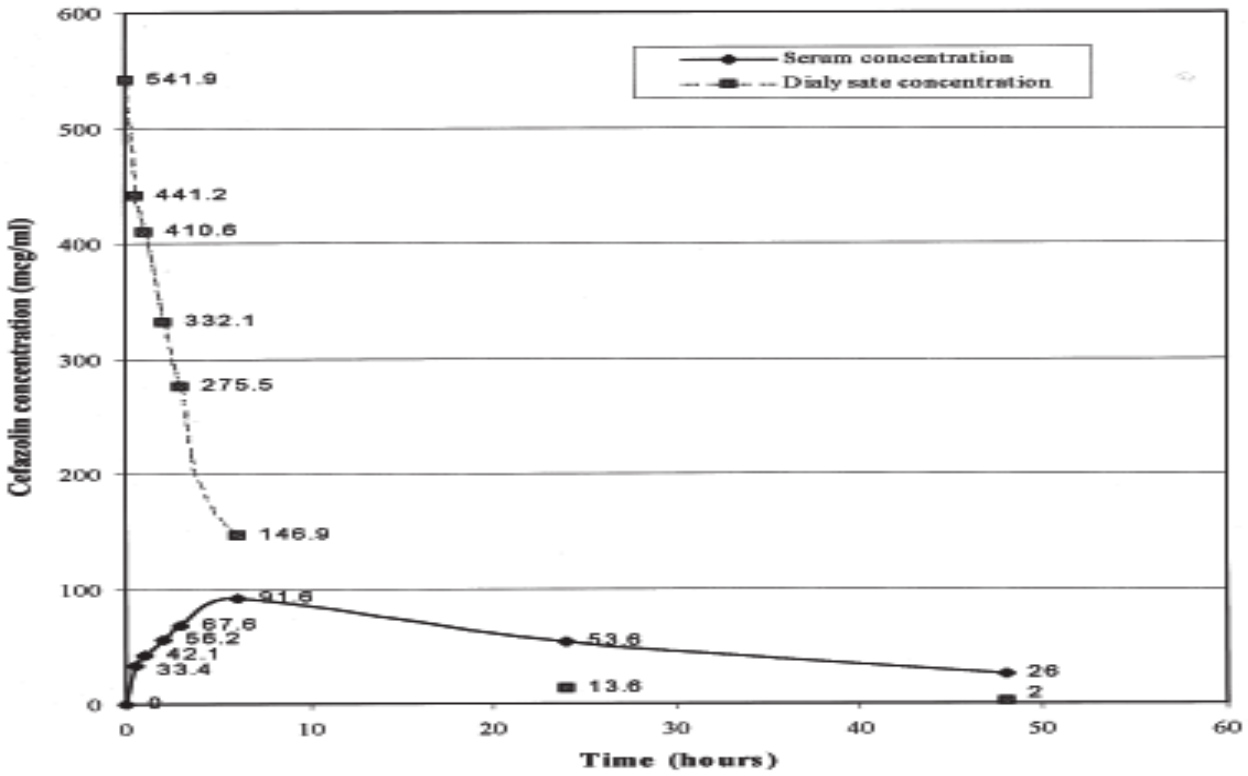

Figure 1 — Serum and dialysate concentrations over time in a representative nonanuric patient.

CONCLUSIONS

- F of 70% (non-peritonitis)
- Cefazolin 15mg/kg IP q day provides adequate serum and dialysate levels over 24 hours for pts on CAPD (4 non-anuric pts, mean GFR of 1.2ml/min/1.73 m2

  (range 0.2 to 1.9)
- Caution for need for increased dosing for pt with higher renal function

Pharmacokinetics of Intermittent Intraperitoneal Ceftazidime

American Journal of Kidney Diseases - Volume 33, Issue 1 (January 1999) - Copyright © 1999 W. B. Saunders Company - About This Journal Remove Journal Issue Alert Add Journal Issue Alert
DOI: 10.1016/S0272-6386%2899%2970265-9

ORIGINAL INVESTIGATIONS

Pharmacokinetics of Intermittent Intraperitoneal Ceftazidime

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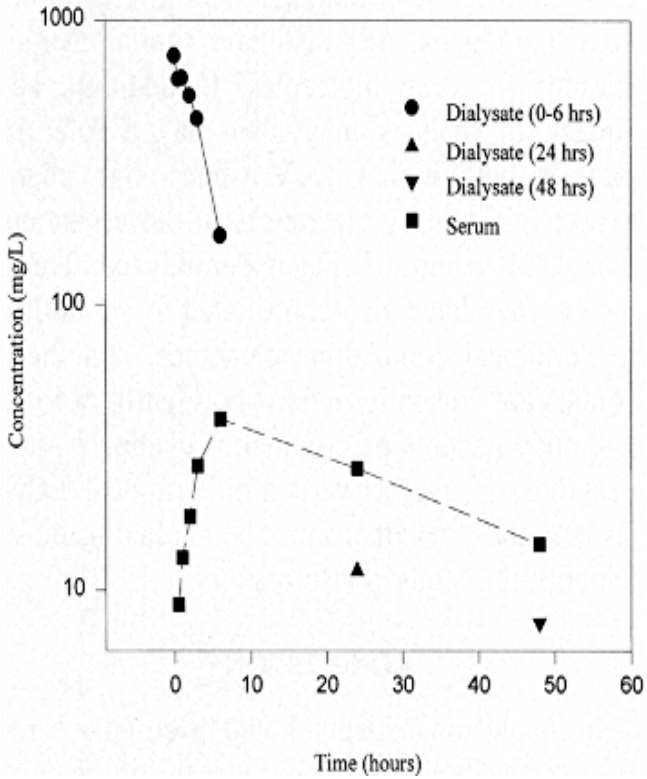
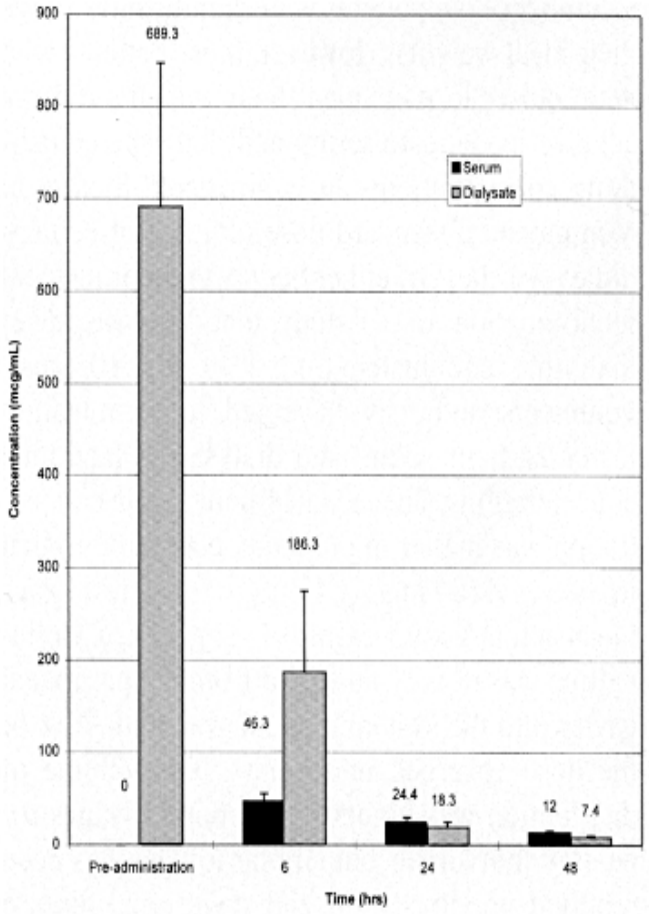
SERUM-DIALYSATE CONCENTRATIONS OVER TIME AFTER CEFTAZIDIME IN CAPD PATIENTS




900
800
700
600
500
400
300
200
100
0
Concentration (mcg/mL)
689.3
186.3
46.3
0
24.4
18.3
12
7.4
Serum
Dialysate
Pre-administration
6
24
48
Time (hrs)

RESULTS

- F : 72% ± 14%
- Vd : 0.34 ± 0.08 L/kg
- T1/2 : 22 ± 5 hours
- CLpd 5.74 ± 1.6 mL/min
- Serum & dialysate concentrations at 24 hours 24 ± 6 mcg/dL and 18 ± 7 mcg/dL, respectively, and were 12.0 ± 3.6 mcg/dL and 7.4 ± 3.1 mcg/dL at 48 hours

CONCLUSIONS

- Intermittent IP ceftazidime (15mg/kg) once daily in CAPD provided adequate serum and dialysate concentrations over 48 hours.
- Lack of similar study in APD patients, but same dosing regimen may produce adequate serum and dialysate concentrations for 24 hours in APD patients

Disposition of Ceftazidime After Intraperitoneal Administration in Adolescent Patients Receiving Continuous Cycling Peritoneal Dialysis

Laura L. Sisterhen, MD, Cindy D. Stowe, PharmD, Hank C. Farrar, MD, Christine K. Blaszak, RN, and Richard T. Blaszak, MD

PK OF CEFTAZIDIME IN ADOLESCENTS ON APD

Table 1. Patient Demographics

Subject No.	Weight (kg)	Height (cm)	Age (y)	Sex	Race	Primary Diagnosis	Peritonitis (prior episodes)	Months on CCPD	Urine Volume (mL)	Residual Renal Function* (mL/min/1.73 m^2)	Renal Clearance of Ceftazidime (mL/min/1.73 m^2)
1	44.2	163	13	M	AA	PUV	0	16	80	0.11	0.10
2	69.5	168	14	M	H	PUV	0	20	2,268	4.85	3.68
3	82.7	168	14	M	H	FSGS	0	8	275	0.92	0.87
4	53	151	18	M	C	PBS	3	12	NA	NA	NA
5	41.8	148	13	F	C	FSGS	3	36	NA	NA	NA
Mean	58.2	159.6	14.4					18.4			
SD	17.5	9.6	2.1					10.8			

NOTE. To convert residual renal function and renal clearance of ceftazidime in mL/min to mL/s, multiply by 0.01667.

Abbreviations: AA, African American; H, Hispanic; C, Caucasian; PUV, posterior urethral valves; FSGS, focal segmental glomerulosclerosis; PBS, prune belly syndrome; NA, not applicable.

*Average clearance of creatinine and urea.

CCPD RX

Table 2. Patient Dialysis Characteristics

Subject No.	Short Cycle Volume (L)	Short Cycle No.	Short Cycle Total Time (h)	Day Fill Volume (L)	Day Fill Total Time (h)	Total Therapy Volume (L)
1	1.8	8	8.1*	0.9	16.8	15.3
2	2.0	8	7.5	0.9	16.5	16.9
3	2.5	6	7.8	1.0	16.2	16
4	1.8	8	7.5	0.9	16	15.3
5	1.6	9	8.6	0.7	15.4	15.1
Mean	1.9	7.8	7.9	0.9	16.2	15.7
SD	0.3	1.1	0.5	0.1	0.5	0.7

*Absolute study times.

PK OF CEFTAZIDIME IN CCPD

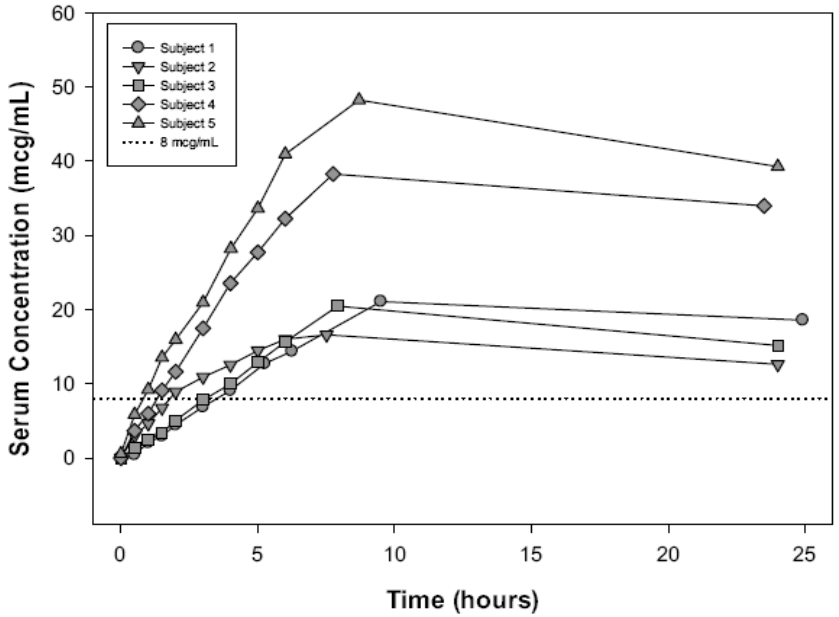


Fig 1. Ceftazidime serum concentration–time profile.

CONCLUSIONS

- Continuous IP dosing of 125mg/L in every exchange in the absence of a loading dose gave adequate serum and dialysate concentrations (>8 mcg/ml) over 24 hours.

Peritoneal Dialysis International, Vol. 21, pp. 378–385
Printed in Canada.

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INTRAVENOUS VANCOMYCIN PHARMACOKINETICS IN AUTOMATED PERITONEAL DIALYSIS PATIENTS

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TABLE 2

Vancomycin Volume of Distribution, Elimination Rate Constant, and Corresponding Half-Life On and Off Cycler

Patient	Mean k_{el} (/hour) Dwells 1–3	Mean t½ (hours) Dwells 1–3	Mean k_{el} (/hour) Dwells 4&5	Mean t½ (hours) Dwells 4&5	Mean k_{sd} (/hour) Dwells 1–3	Mean t½ k_{sd} (hours) Dwells 1–3	Vd (L/kg)
1	0.19	9.7	0.01	63.0	0.23	3.0	0.1
2	0.07	9.8	0.02	34.7	0.15	4.5	0.3
3	0.17	5.7	0.01	57.8	0.25	2.8	0.3
4	0.09	9.9	0.02	38.5	0.14	5.1	0.3
5	0.07	17.7	0.03	25.7			0.3
6	0.11	6.7	0.01	115.5	0.28	2.5	0.5
7	0.12	8.8	0.01	86.6	0.51	1.4	0.5
8	0.09	12.0	0.01	86.6	0.42	1.6	0.4
9	0.07	22.8	0.03	20.4	0.40	1.7	0.5
10	0.11	12.7	0.01	99.0	0.28	2.5	0.4
Mean	0.11	11.6	0.02	62.8	0.30	2.8	0.4
SD	0.09	5.2	0.01	33.0	0.12	1.3	0.1

k_{el} = serum elimination rate; t½ = half-life; k_{sd} = serum-to-dialysate transfer rate; Vd = volume of distribution.

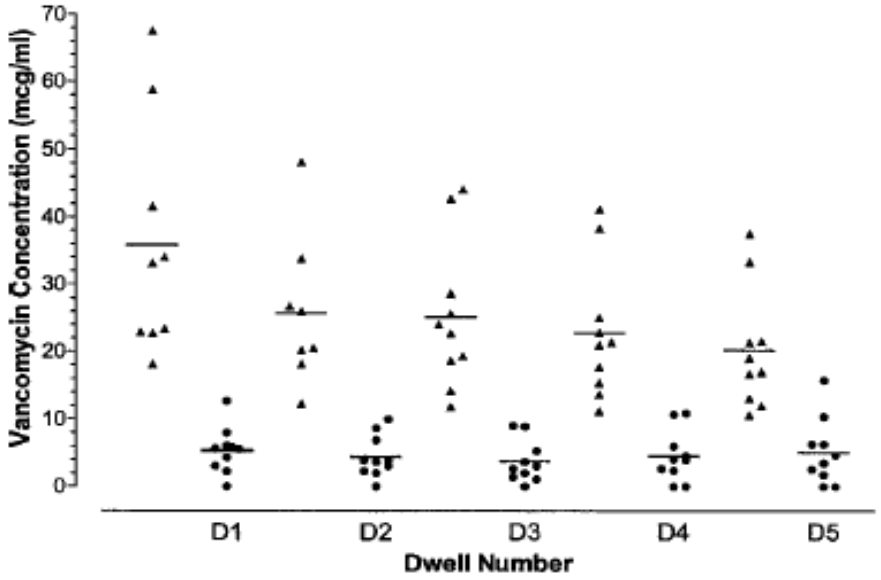

Figure 1 – Mean vancomycin serum (closed triangles) and dialysate (closed circles) end-of-dwell concentrations.

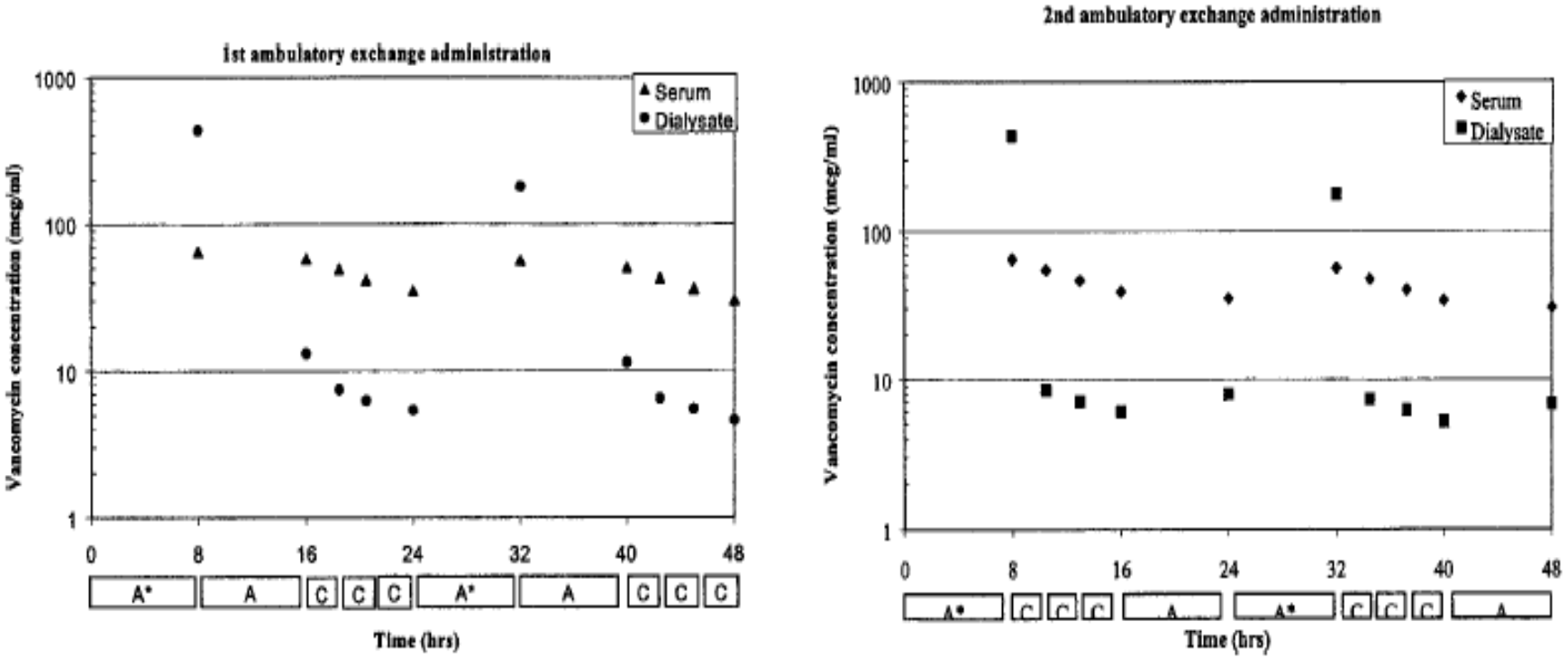

Figure 2 – Model-predicted vancomycin serum and dialysate concentrations at end of dwell if administered intraperitoneally during the first or second ambulatory dwell in a 70-kg individual. A = ambulatory; C = cycler; * = vancomycin administered.

VANCOMYCIN PHARMACOKINETICS IN PATIENTS RECEIVING APD

TABLE 2

Vancomycin Volume of Distribution, Elimination Rate Constant, and Corresponding Half-Life On and Off Cycler

Patient	Mean k_{el} (/hour) Dwells 1-3	Mean t½ (hours) Dwells 1-3	Mean k_{el} (/hour) Dwells 4&5	Mean t½ (hours) Dwells 4&5	Mean k_{sd} (/hour) Dwells 1-3	Mean t½ k_{sd} (hours) Dwells 1-3	Vd (L/kg)
1	0.19	9.7	0.01	63.0	0.23	3.0	0.1
2	0.07	9.8	0.02	34.7	0.15	4.5	0.3
3	0.17	5.7	0.01	57.8	0.25	2.8	0.3
4	0.09	9.9	0.02	38.5	0.14	5.1	0.3
5	0.07	17.7	0.03	25.7			0.3
6	0.11	6.7	0.01	115.5	0.28	2.5	0.5
7	0.12	8.8	0.01	86.6	0.51	1.4	0.5
8	0.09	12.0	0.01	86.6	0.42	1.6	0.4
9	0.07	22.8	0.03	20.4	0.40	1.7	0.5
10	0.11	12.7	0.01	99.0	0.28	2.5	0.4
Mean	0.11	11.6	0.02	62.8	0.30	2.8	0.4
S D	0.09	5.2	0.01	33.0	0.12	1.3	0.1

k_{el} = serum elimination rate; t½ = half-life; k_{sd} = serum-to-dialysate transfer rate; Vd = volume of distribution.

CONCLUSIONS

- Clearance of vancomycin by APD regimen is much more significant compared to CAPD clearance
- To maintain adequate serum and dialysate concentrations over 24 h, need a 35 mg/kg IP dose day1, assuming a bioavailability of 65%, followed by 15mg/kg IP thereafter every 3 to 5 days to maintain serum concentration >15 mcg/ml.
- Authors cautioned that to maintain adequate dialysate levels throughout treatment, serum concentrations are sustained 30-60 mcg/ml for long periods of time
- Consider switching pt to CAPD or limit cycles to 3 or less

Peritoneal Dialysis International, Vol. 27, pp. 79–85
Printed in Canada.

0896-8608/07 $3.00 + .00

VANCOMYCIN DISPOSITION FOLLOWING INTRAPERITONEAL ADMINISTRATION IN CHILDREN RECEIVING PERITONEAL DIALYSIS

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TABLE 1
Demographic Data

Patient	Age (years)	Gender	Weight (kg)	BSA (m^2)	PET (D/P urea)	PD duration (months)	Peritonitis episodes (*n*)
1	14	M	41	1.25	High	83	3
2	10	F	25	0.88	High-average	29	0
3	16	F	59	1.63	Low-average	3	0
4	5	F	26	0.88	High-average	58	0
5	13	F	43	1.4	Low-average	16	0
6	17	M	89	2.2	High-average	10	0
7	14	M	25	0.94	High-average	8	0

BSA = body surface area; PET = peritoneal equilibrium test; D/P = dialysate-to-plasma ratio; PD = peritoneal dialysis.

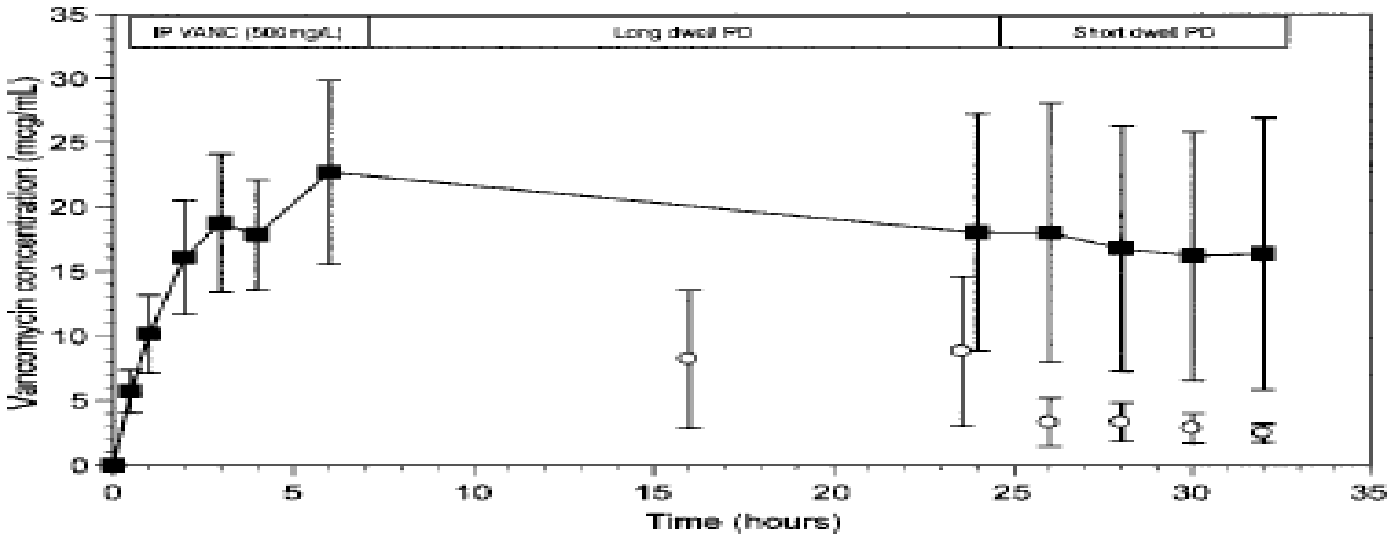

Figure 1 — Serum (closed squares) and dialysis effluent (open circles) vancomycin (VANC) concentration (mean ± SD) versus-time curve following a 6-hour intraperitoneal (IP) exchange (1100 mL/m^2) containing vancomycin 500 mg/L. The dialysate effluent (open circles) concentration during short-dwell peritoneal dialysis (PD) represents the vancomycin concentration at 90 minutes.

D/P VANCOMYCIN AND PET

TABLE 3
Individual Vancomycin Dialysate-to-Plasma (D/P) Ratios, Vancomycin Cl_{PD}, and Peritoneal Equilibrium Test (PET) Results

Patient	Vancomycin D/P ratio 90-minute	Vancomycin D/P ratio 8-hour	Vancomycin Cl_{PD} (mL/min/1.73 m^2)	PET
1	0.31	0.73	4.54	High
2	0.29	0.56	3.24	High-average
3	0.19	0.44	3.26	Low-average
4	0.12	0.19	1.53	High-average
5	0.17	0.20	1.90	Low-average
6	0.08	0.48	1.80	High-average
7	0.39	0.58	3.19	High-average
Mean±SD	0.22±0.11[a]	0.45±0.20[b]	2.78±1.08	

Cl_{PD} = clearance attributable to peritoneal dialysis [$(Cl_{CAPD} + Cl_{APD})/2$].
[a] Correlation with vancomycin Cl_{PD}: $r = 0.76$ ($p < 0.05$).
[b] Correlation with vancomycin Cl_{PD}: $r = 0.86$ ($p < 0.05$).

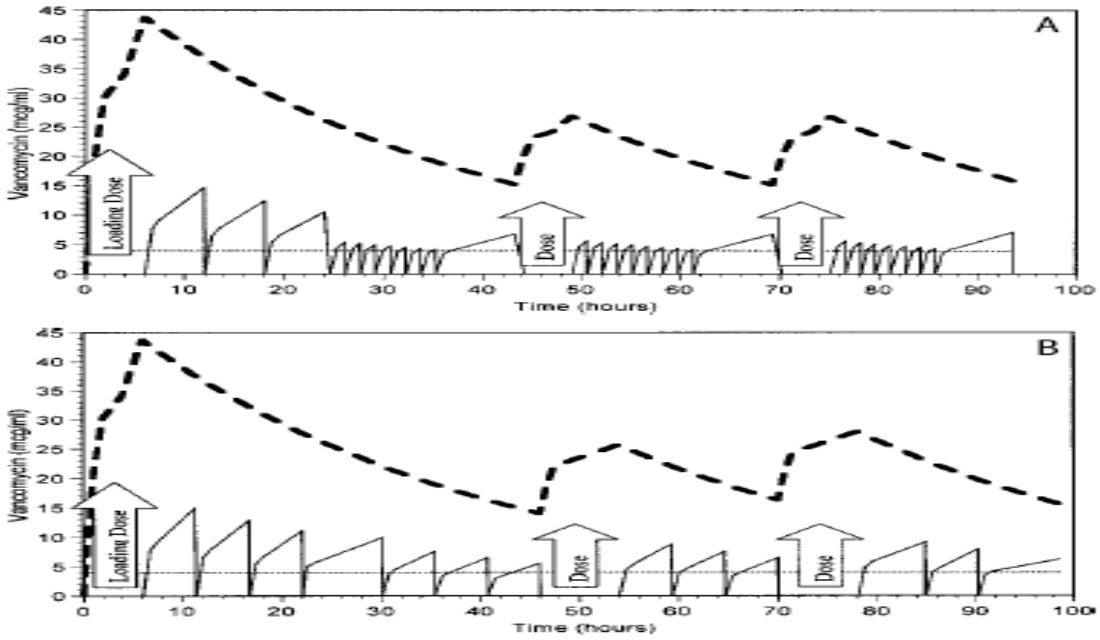

Figure 2 — Serum (dashed line) and dialysis effluent (solid line) vancomycin concentration-versus-time curve modeled for a child receiving automated peritoneal dialysis (A) and for a child receiving continuous ambulatory peritoneal dialysis (B) following a 6-hour intraperitoneal exchange (1100 mL/m^2) containing vancomycin 1000 mg/L and then 250 mg/L once daily from day 2 forward.

DISCUSSION

- Vancomycin total CL is higher than in adults
- Molecular wt important in explaining the lack of correlation of CLpd of vancomycin with PET D/P urea as vancomycin is much larger molecule (1480 D) compared with urea
- During short dwell, serum concentrations must be at least 18 mcg/ml to achieve 4 mcg/ml in dialysate at the end of dwell for APD
- CAPD, target serum concentration > 9 mcg/ml to keep dialysate concentration >4 mcg/ml
- IP 30mg/kg, followed by 7.5mg/kg IP daily from day 2 to end of treatment

Peritoneal Dialysis International, Vol. 25, pp. 380–386
Printed in Canada.

0896-8608/05 $3.00 + .00

PHARMACOKINETICS OF INTRAPERITONEAL CEFEPIME IN AUTOMATED PERITONEAL DIALYSIS

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TABLE 2
Pharmacokinetic Parameters for Cefepime in Patients on Automated Peritoneal Dialysis (APD)

Patient	F (%)	V_d (L/kg)	k_{d-s} (/hr)	$t½_{d-s}$ (hr)	k_{el} (/hr)	t½ (hr)	CL_{total} (mL/min)	CL_{APD} (mL/min)	CL_{renal} (mL/min)
1	88.1	0.32	0.246	2.8	0.036	19.1	14.3	4.5	Anuric
2	82.4	0.41	0.240	2.9	0.044	15.6	23.5	3.9	6.6
3	82.1	0.29	0.238	2.9	0.061	11.4	17.8	4.1	3.8
4	93.9	0.43	0.352	2.0	0.060	11.5	18.2	5.1	4.8
5	84.2	0.32	0.265	2.6	0.047	14.6	14.3	3.4	1.6
6	75.4	0.26	0.285	2.4	0.064	10.9	10.8	5.1	0.5
Mean±SD	84.3±6.2	0.34±0.07	0.271±0.043	2.6±0.4	0.052±0.011	13.8±3.2	16.5±4.4	4.3±0.7	3.5±2.5

F = systemic bioavailability; V_d = systemic volume of distribution; k_{d-s} = rate constant for absorption from dialysate to serum; $t½_{d-s}$ = half-life of drug absorption from the peritoneal cavity; k_{el} = serum elimination rate constant; t½ = half-life of drug elimination from the serum; CL_{total} = total drug clearance; CL_{APD} = peritoneal dialysis clearance; CL_{renal} = renal clearance.

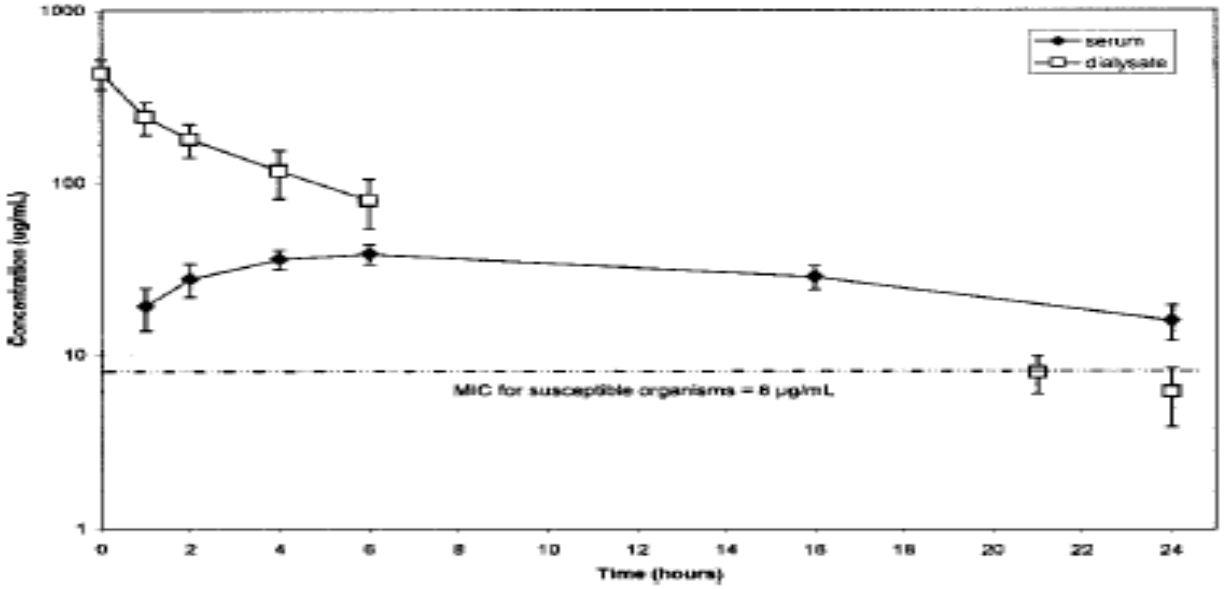

Figure 1 — Serum and dialysate cefepime concentrations. [Note: All patients had a dry peritoneal cavity from $t = 6$ hours until $t = 16$ hours. The serum concentration at $t = 16$ was estimated. The dialysate concentration at $t = 21$ represents pooled dialysate from the first two overnight dwells.]

TABLE 3

Mean (±SD) Estimated Maximum (Css max) and Minimum (Css min) Steady State Serum Concentrations Calculated Assuming First-Order Elimination Pharmacokinetic Equations (Appendix B)

	Daily peritoneal dialysis regimen			
	APD[a]		CAPD[b]	
Intraperitoneal cefepime dose	1000 mg q 24 hr	1000 mg q 48 hr	1000 mg q 24 hr	1000 mg q 48 hr
Css max (µg/mL)	51.0±11.8	39.6±10.1	58.5±16.8	42.3±12.1
Css min (µg/mL)	14.9±5.0	3.5±1.9	22.4±6.4	6.2±1.8

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; q = every.

[a] APD = one 6 hour cefepime-containing daytime dwell followed by three automatically instilled dwells exchanged every 2.5 hours over approximately 8 hours (dialysate = 2.5% dextrose; 2 L per exchange).

[b] CAPD = one 6 hour cefepime-containing dwell followed by four exchanges performed manually approximately every 6 hours (dialysate = 2.5% dextrose; 2 L per exchange).

- Dosing & monitoring

COMPARISON OF CAPD AND APD PK

TABLE 1. Intermittent IP antibiotic half-lives and pharmacokinetic model predictions for APD

		Dwell time (hours)		Antibiotic half-life (hours)		
Antibiotic/references	Dose (mg/kg IV)	On cycler	Off cycler	On cycler	Off cycler	Model prediction
Cefazolin (4 M, 4 F)/7	15	2.5 ± 0.2	7.7 ± 0.4	10.7 ± 4.7	23.1 ± 5.6[b]	20 mg/kg IP once a day, in first or second ambulatory dwell
Tobramycin (6 M, 4 F)/7	0.6	2.5 ± 0.2	7.7 ± 0.4	14.3 ± 4.5	68.5 ± 26.5[b]	Loading dose 1.5 mg/kg IP day 1; maintenance dose 0.5 mg/kg IP once a day, in first or second ambulatory dwell
Vancomycin (4 M, 6 F)/8	15	2.3 ± 0.1	7.3 ± 0.1	11.6 ± 5.2	62.8 ± 33[c]	Loading dose 35 mg/kg IP; maintenance dose 15 mg/kg IP once a day. Use caution: see text.
Piperacillin (3 M, 5 F)/9	35	2.25 ± 0.1	7.26 ± 0.1	1.99 ± 0.39	4.39 ± 5.4	4000 mg IV twice a day
Fluconazole (3 M, 2 F)/10	200 mg[a]	Five to six exchanges over 12 hours	12 hours	71.65 ± 12.76[d]		200 mg IP every 24–48 hours

IP, intraperitoneal; APD, automated peritoneal dialysis; IV, intravenous; M, male; F, female.
[a] Dose not weight based. All patients received 200 mg IP.
[b] $p = 0.001$.
[c] $p < 0.001$.
[d] Overall half-life reported which includes times that patients were on and off cycler.

PDCL IN CAPD AND APD

TABLE 2. Comparison of various antibiotic peritoneal clearances in CAPD and APD patients

	Dialysate flow (ml/hr)		Peritoneal clearance (ml/min/1.73 m^2)	
Antibiotic/references	APD	CAPD	APD	CAPD
Cefazolin/7,11	416.7	333.3	2.2 ± 0.7	1.0 ± 0.3
Tobramycin/7,12	416.7	333.3	4.2 ± 0.9	1.1 ± 0.8
Vancomycin/8,13	416.7	333.3	2.1 ± 0.7	1.2 ± 0.5
Piperacillin/9,14	416.7	333.3	5.3 ± 1.1	3.6
Fluconazole/10 (15)	500–687.5		11 ± 2.7	4.3–5.5

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

DOSING CONSIDERATIONS IN APD

- Underdosing is a concern in APD because of increased clearance especially in intermittent IP dosing
- ISPD guidelines for APD include higher doses for APD pt based on published studies
- Pt with higher residual renal function, dosing needs to be individualized with closer monitoring for efficacy/ toxicity
- Important to maintain adequate serum concentrations for transfer of antibiotic from serum to dialysate during drug-free exchange

DIALYSATE LEVELS AND OUTCOMES

- In a study, serum concentrations of ceftazidime were above MIC, whereas dialysate concentrations were < MIC for several hours on day 1 and day 4. Response rate 90%, apparently suggesting that achieving complete therapeutic dialysate concentrations may not be necessary for treatment to be effective
- Difficult to interpret depending on the organisms, susceptibility profile.
- Efficacy may reflect a function of AUC over time rather than a short duration of concentration below MIC

MONITORING

- Clinical symptoms
  - Resolution of abdominal pain
  - Fever
  - Nausea/vomiting
  - Hypotension
  - Clearing of dialysate
  - Blood and dialysate culture

  Catheter removal
  - Drug levels
  - Vancomycin (keep serum > 15 mcg/ml to have dialysate > 4mcg/ml)
  - Gent/Tobramycin (dialysate > 1mcg/ml, difficult to achieve without concerns of accumulation and toxicity)

CONCLUSIONS

- ISPD dosing recommendations are based on PK studies performed in volunteer pt without peritonitis and with fixed dialysis Rx
- Efficacy studies using ISPD recommended doses lacking available
- As pharmacists, we have the expertise to predict serum and dialysate concentrations with dose changes and in the best position to recommend the best dosing regimen and monitoring parameters for the management of peritonitis based on the currently available studies
- Encourage more PK studies of other antibiotics in APD to add to the existing ISPD guidelines

QUESTIONS?