The Physiology of Peritoneal Dialysis As Related To Drug Removal

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Clearance By Dialysis

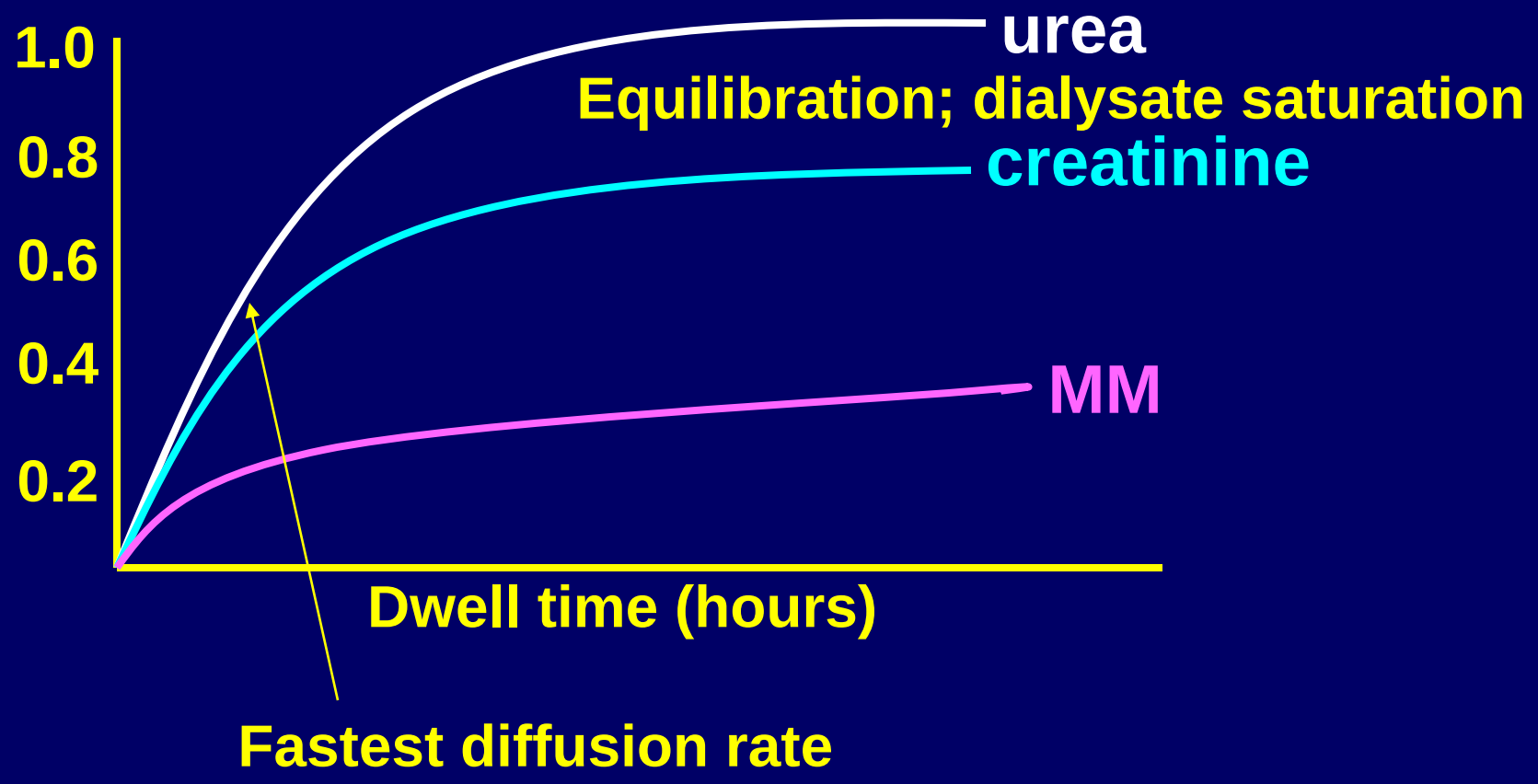
$$\text{Clearance} = \frac{\text{Dialysate concentration}}{\text{Plasma concentration}} \times Qd$$

or

D/P times effuent vol/time

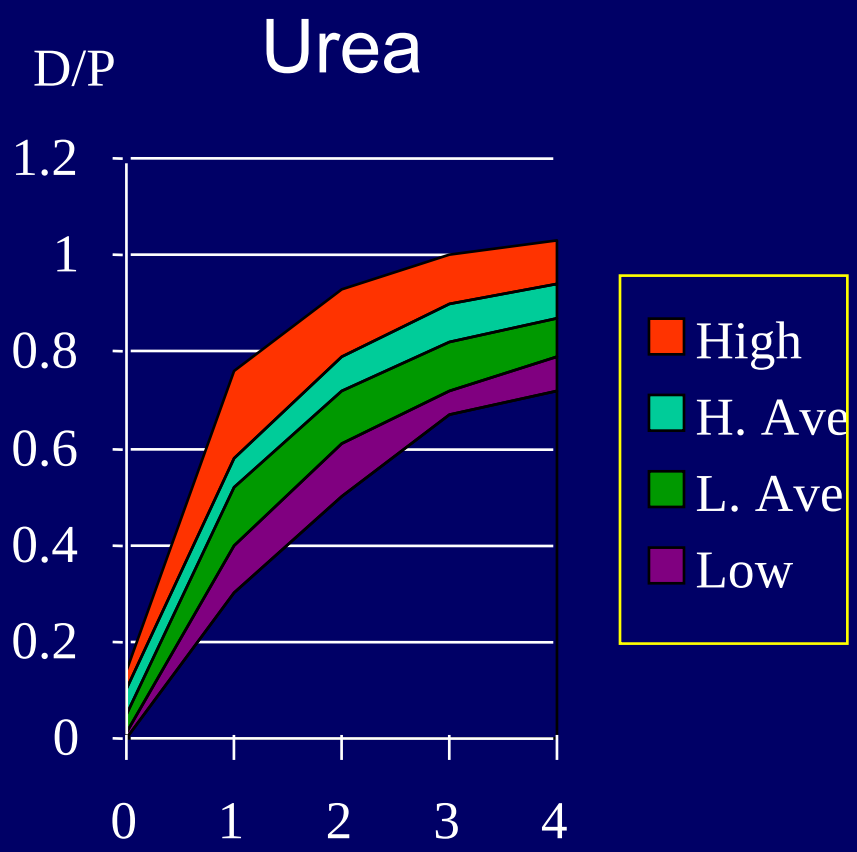
Diffusion Curves

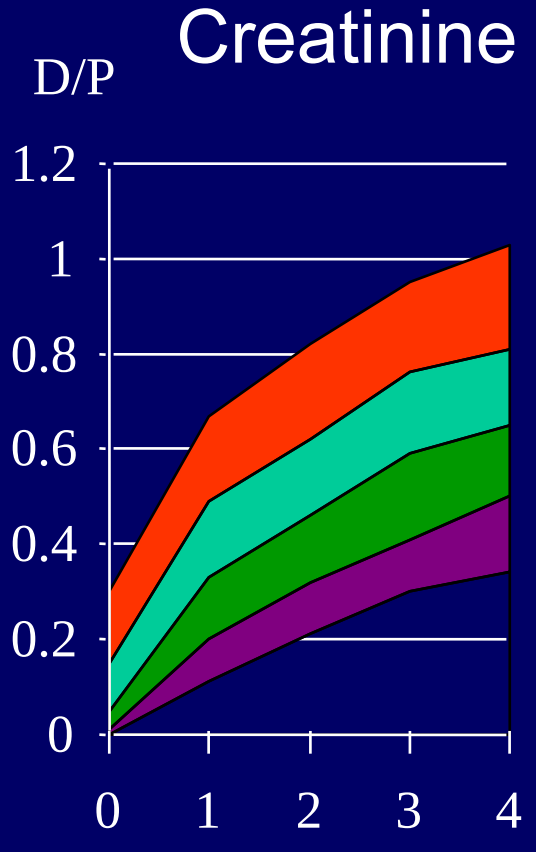
Dialysate to Plasma (D/P) concentration ratios



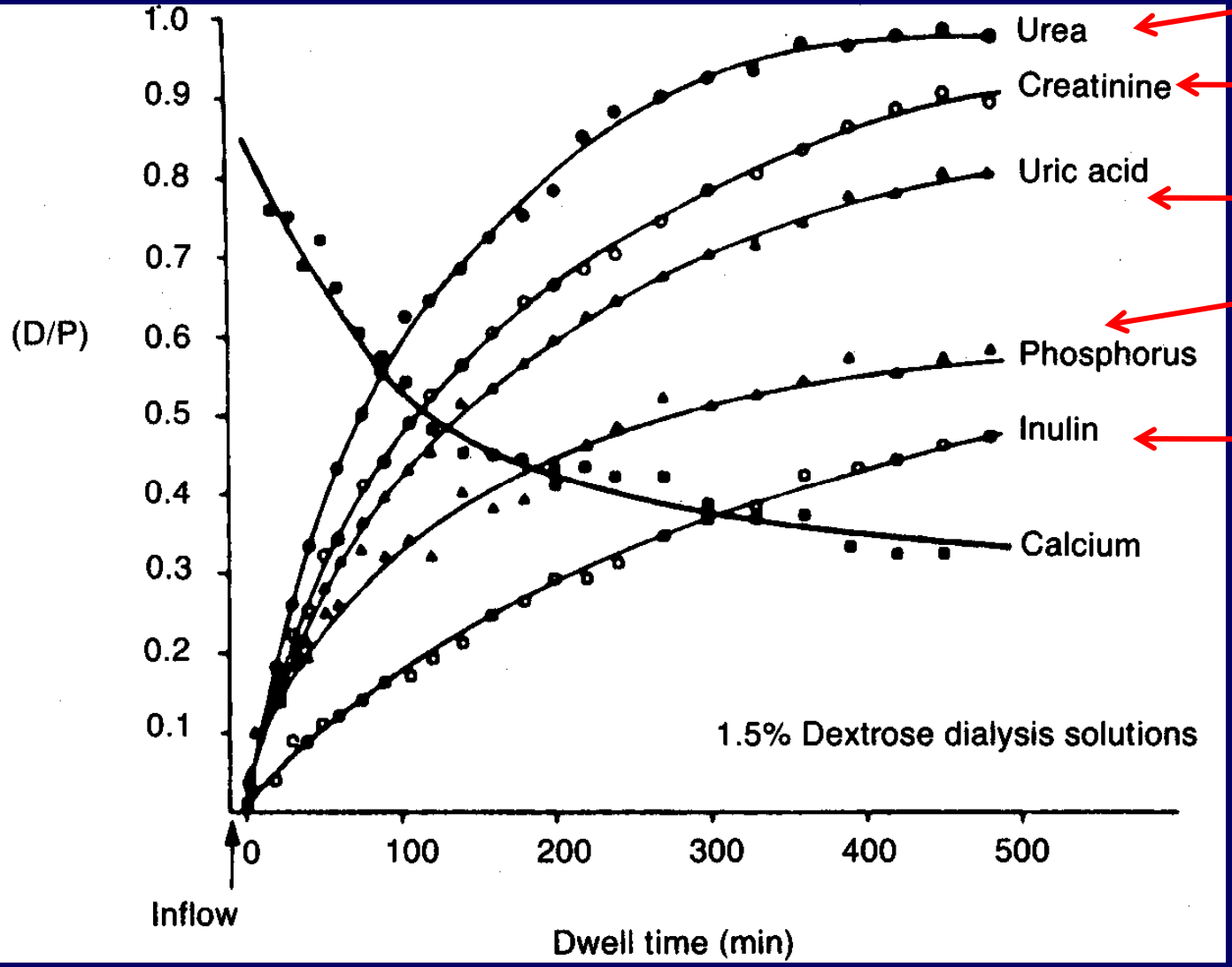
Peritoneal Equilibration Test

Twardowski et al. Perit Dialy Bull 7:138, 1987





D/P And Molecular Size



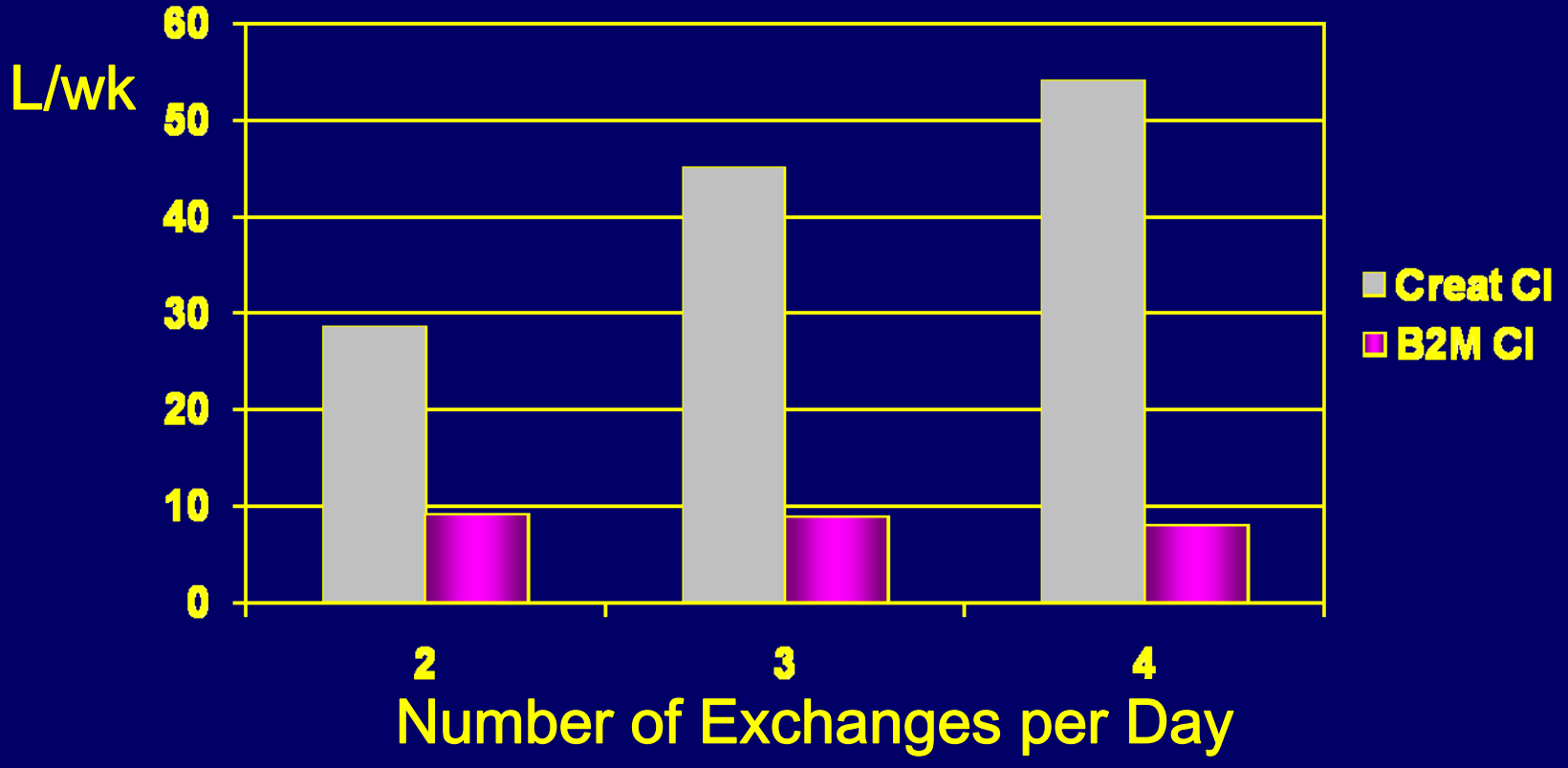
60 daltons

120 daltons

< 100 daltons but act larger due to charge

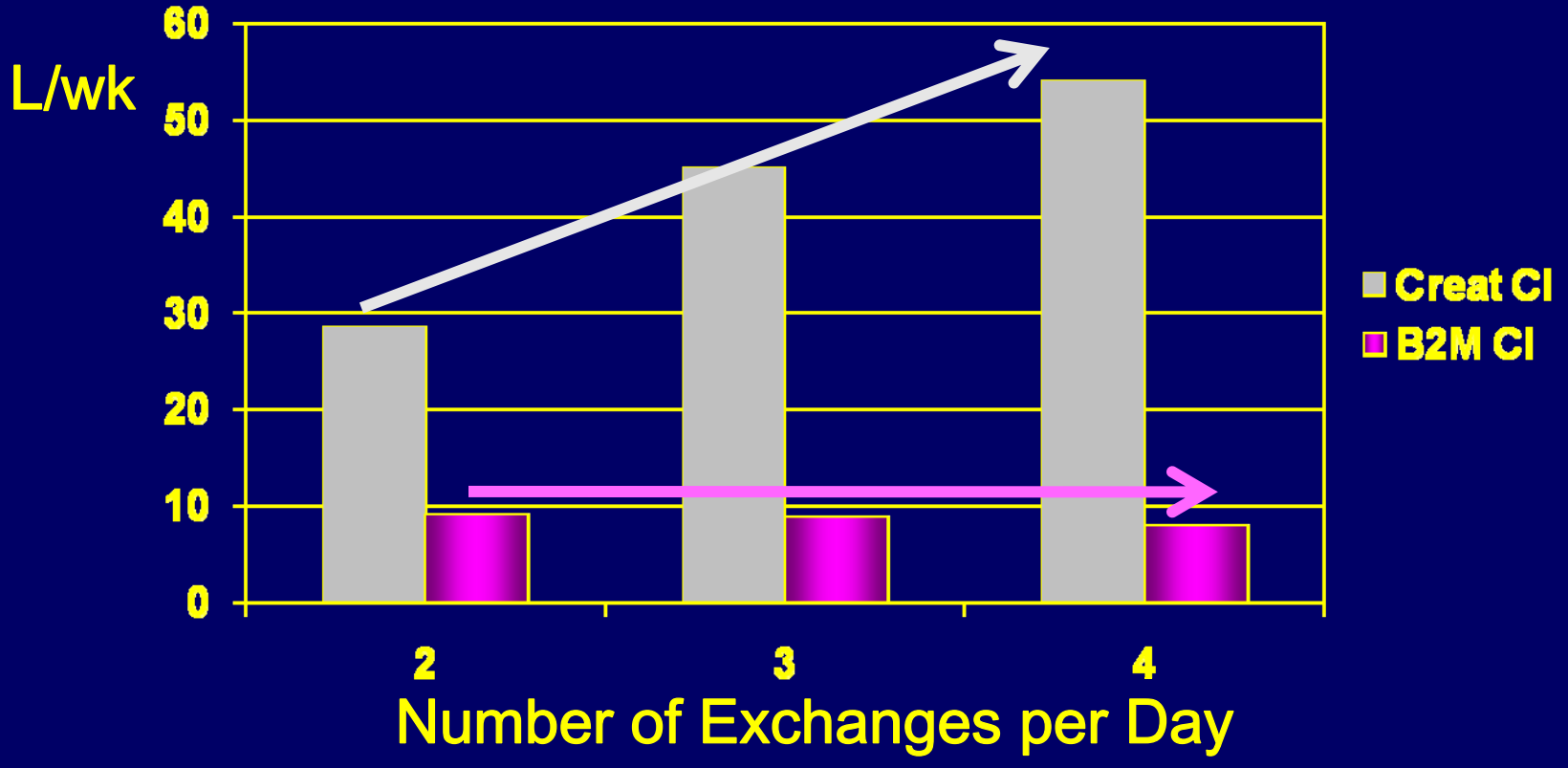
5000 daltons

Dissociation Between Clearance of Small and Middle Molecular Weight Toxins



Kim et al, NDT 21:462, 2001

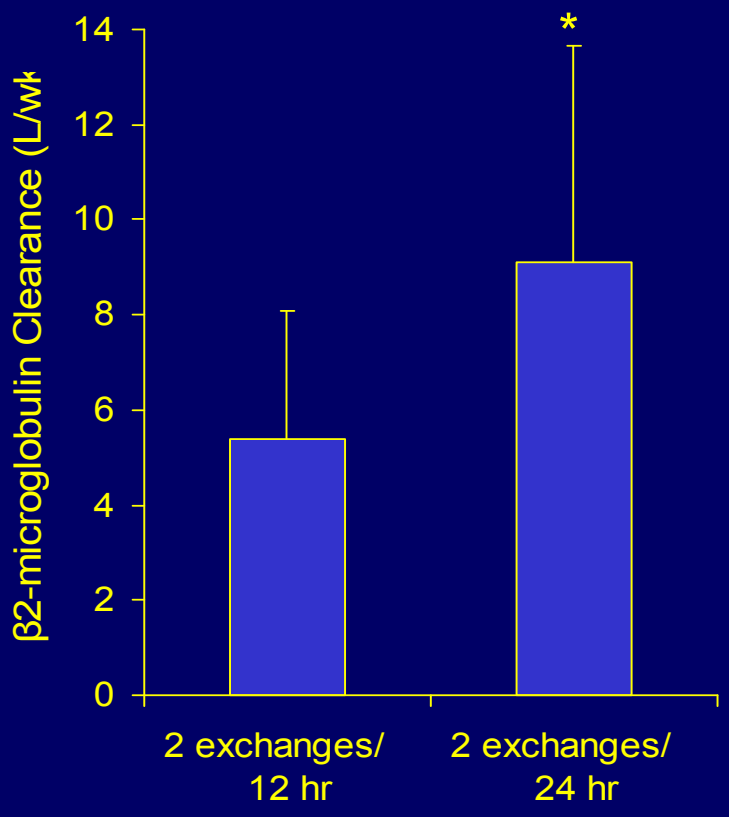
Dissociation Between Clearance of Small and Middle Molecular Weight Toxins

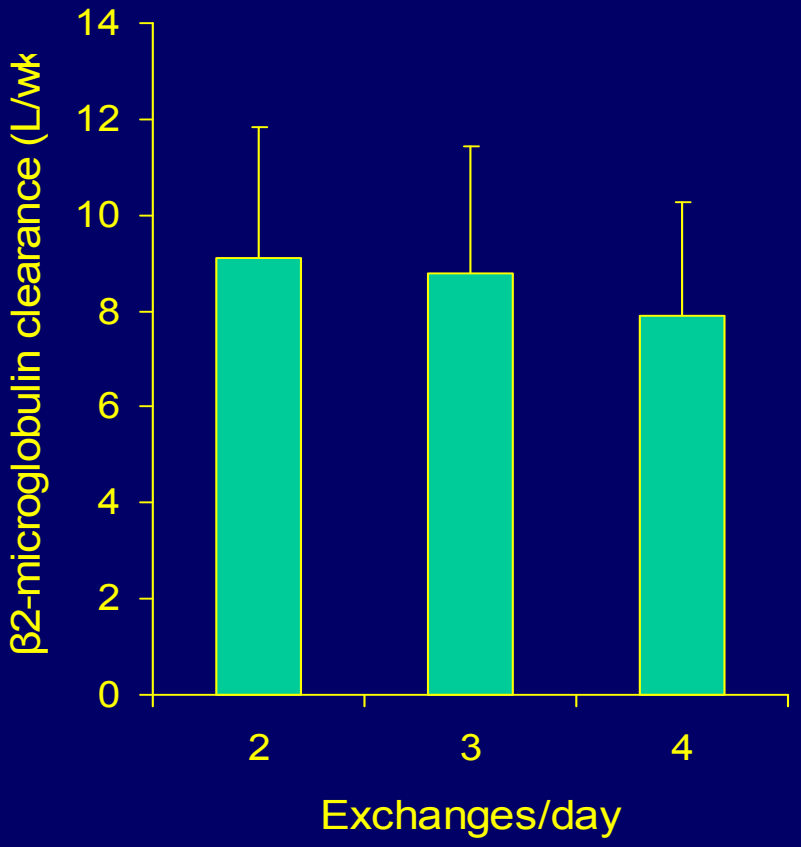


Kim et al, NDT 21:462, 2001

Middle Molecule Clearance Is Dwell Time Dependent

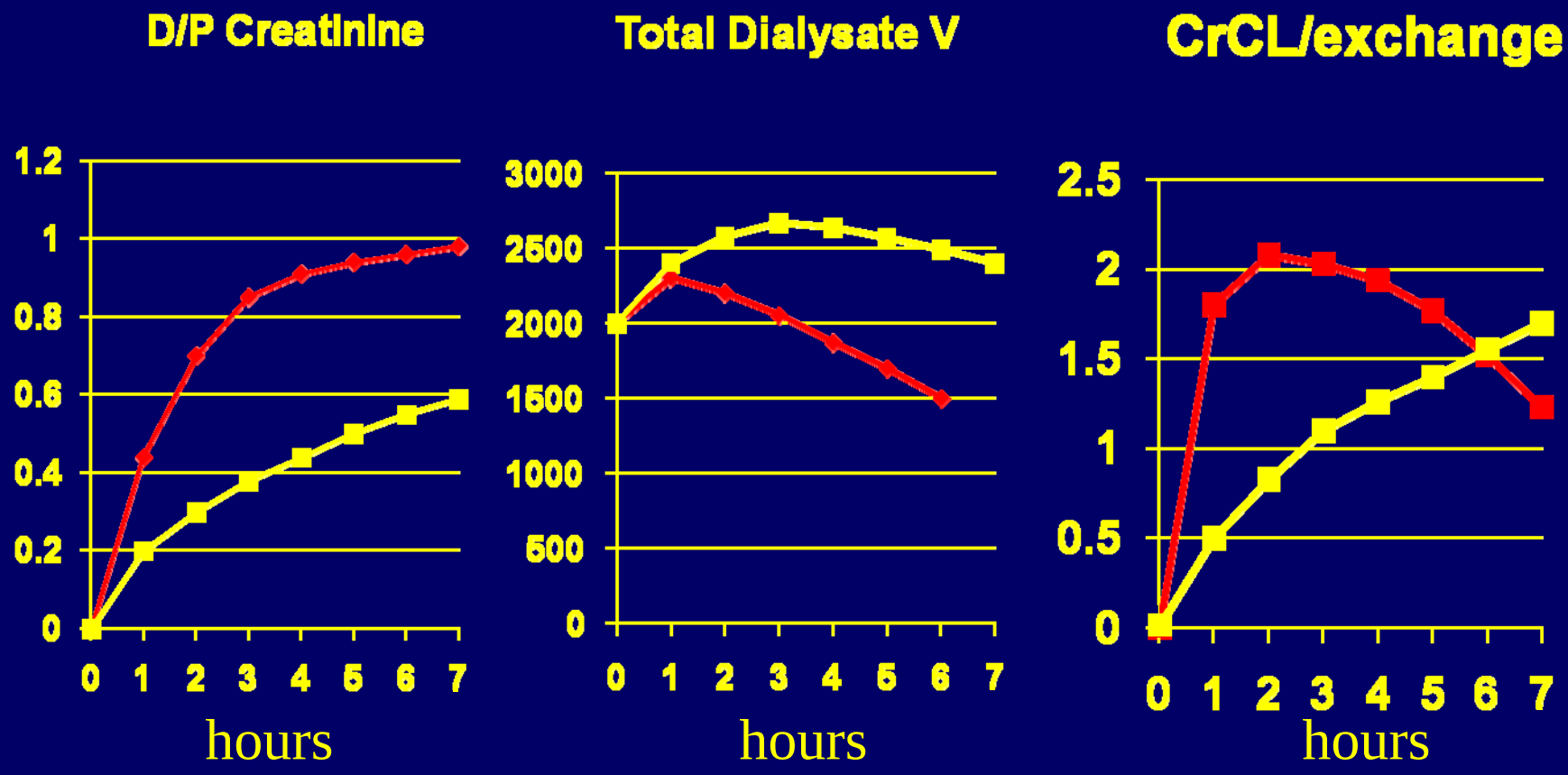
Kim et al. NDT 21:462, 2001





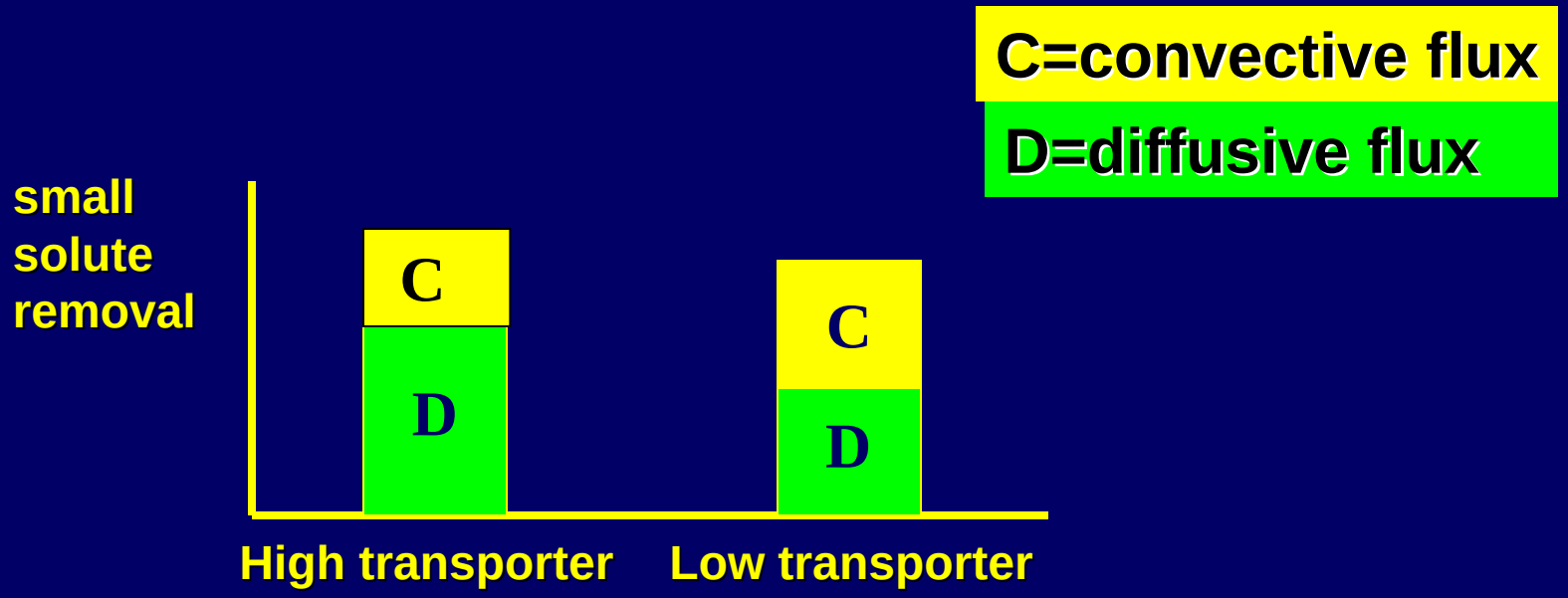
**P* <.05 vs 2 exchanges/12 hr.

Relationship Between Time, Transport Type & Clearance



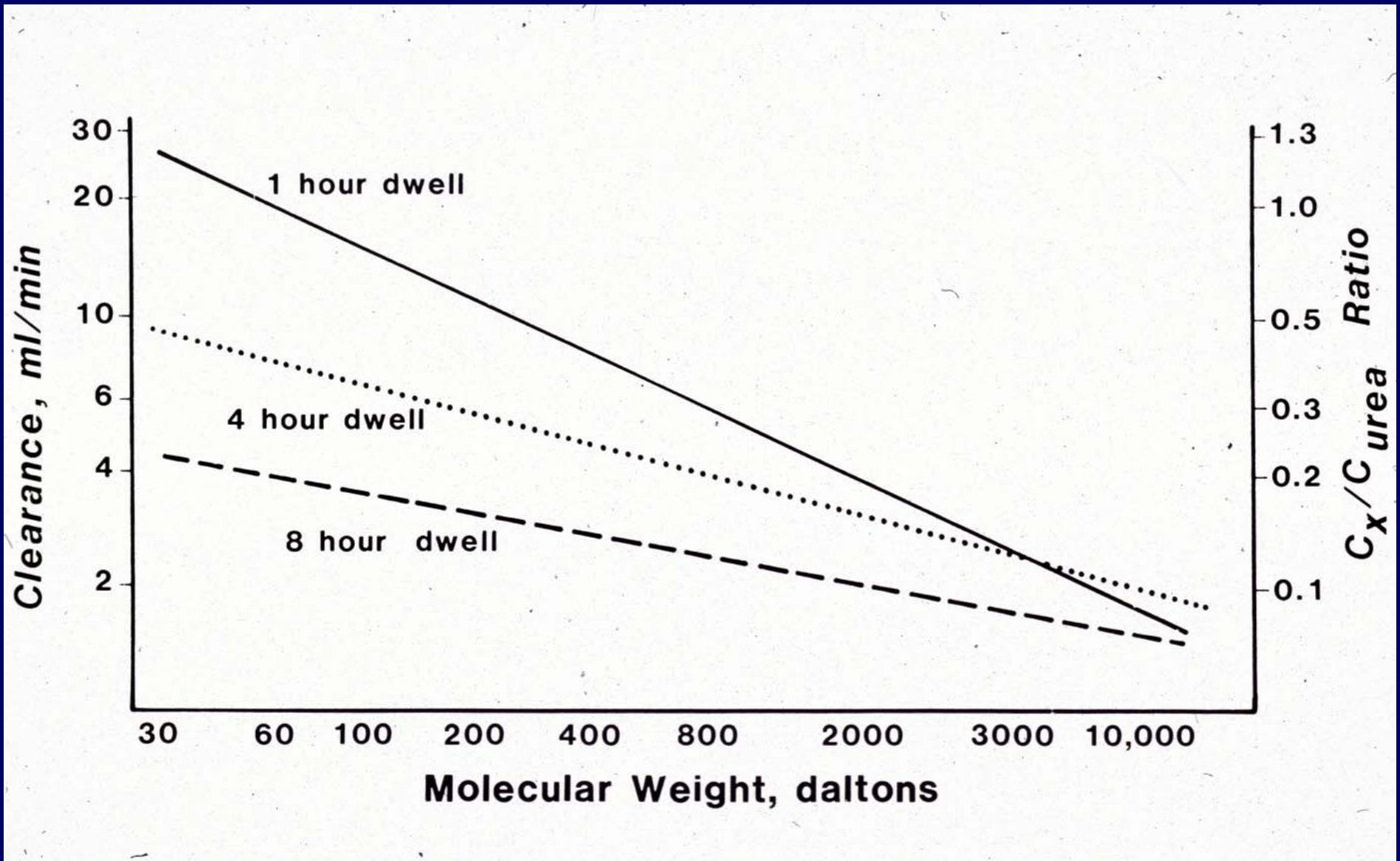
High vs. Low Transporters: Why Solute Removal Is Similar

- **The better UF in the low transporters will increase solute removal through convective transport**

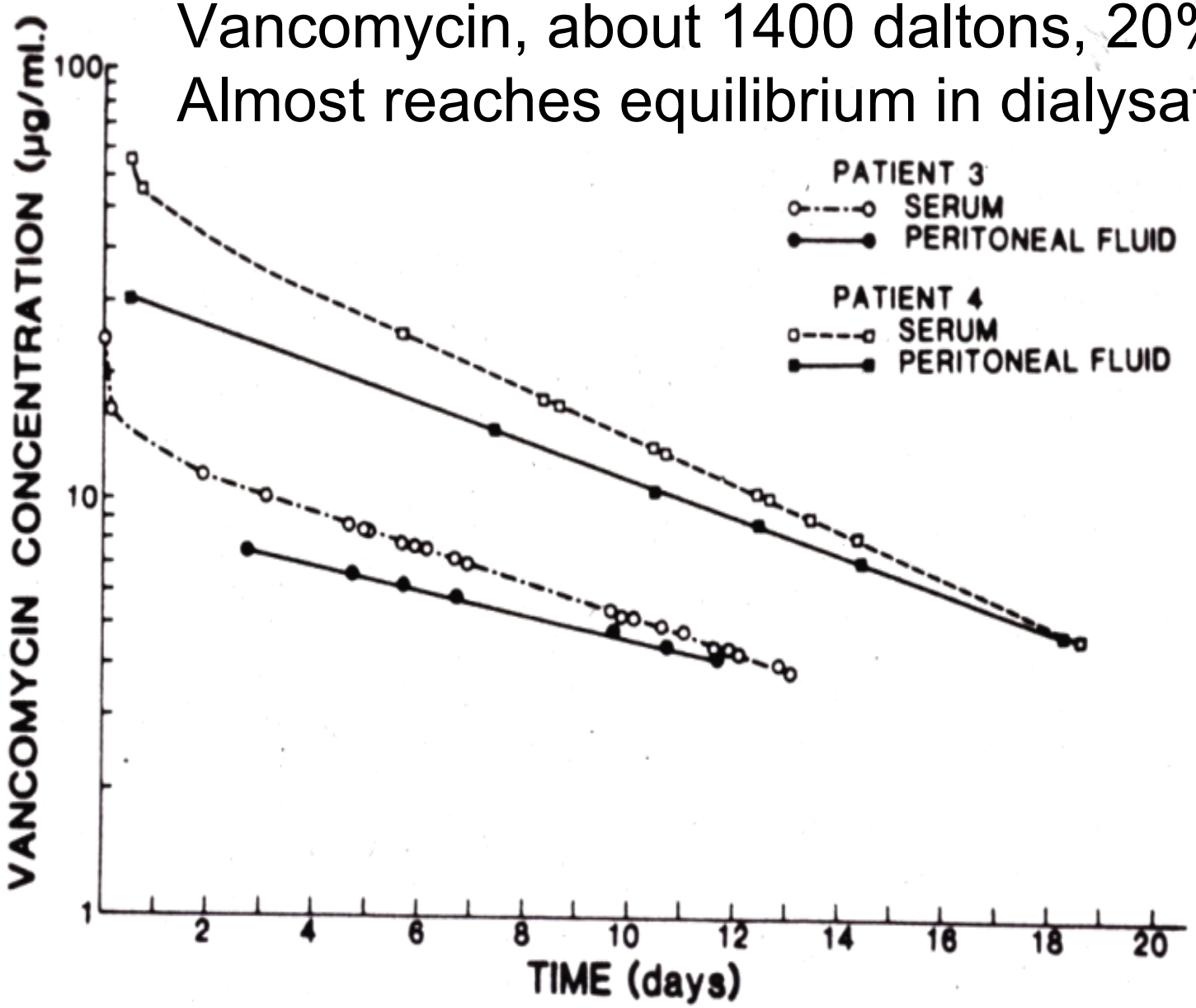


Extrapolations From Jack Maher

Lasrich et al ASAIO Journal 2: 107-113, 1979



Vancomycin, about 1400 daltons, 20% free
Almost reaches equilibrium in dialysate



Vancomycin elimination profiles in serum and peritoneal fluid after a single 1-g (patient 3) or 2
(patient 4) i.v. dose.

Maximum Solute Clearance Is That of Urea So Typically…..

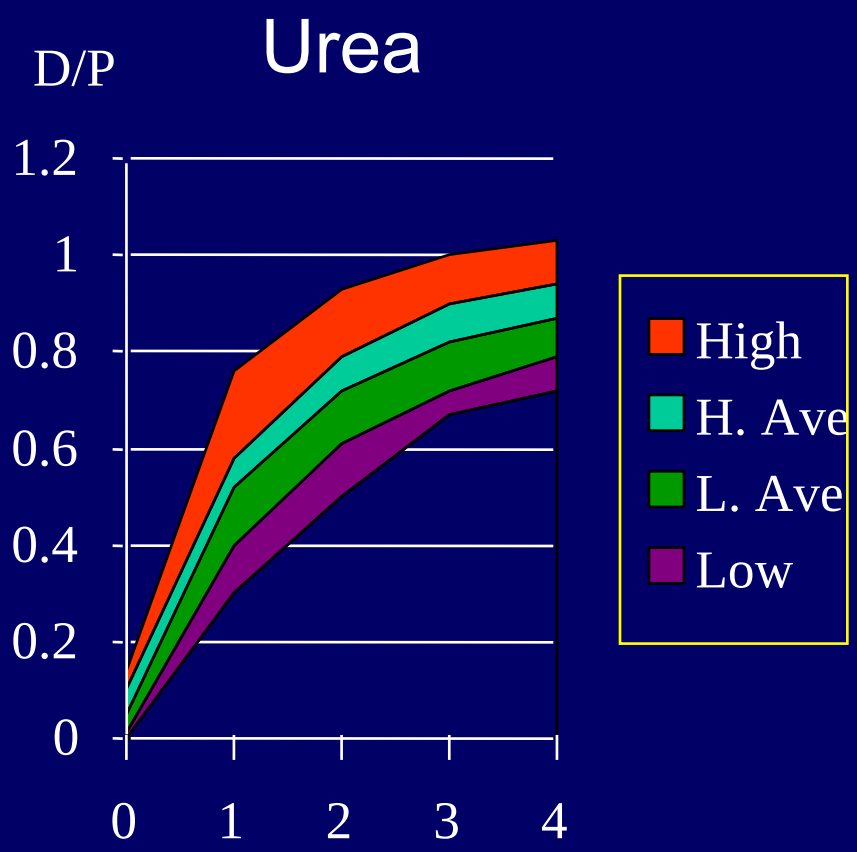
- Small, unbound, uncharged, freely permeable, accessible volume of distribution
- Most anuric PD pts have a weekly Kt/V of < 2.1 or 0.3 per day, Kt/V = 0.3 per day
- Assume V is 35 liter (35,000mL)

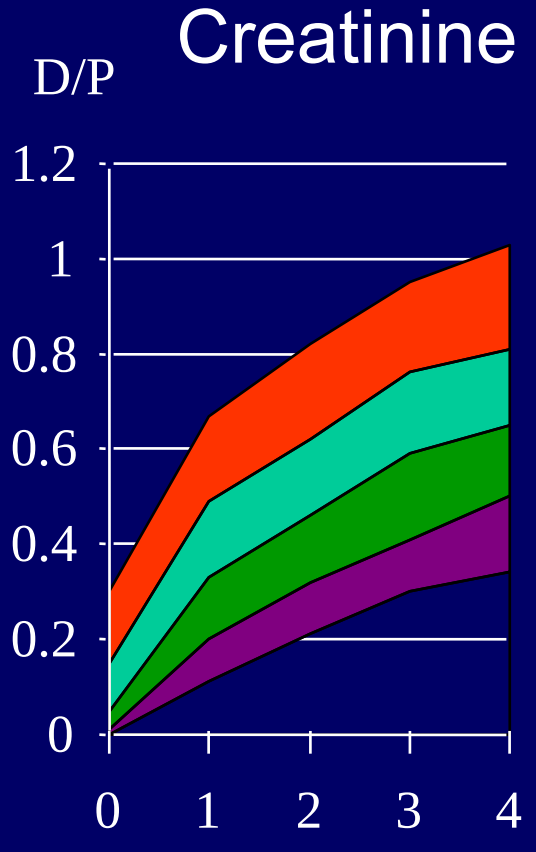
$$\frac{K \times 1440 \text{ min/d}}{35000 \text{ mL}} = 0.3$$

K = 7.3 mL/min

Peritoneal Equilibration Test

Twardowski et al. Perit Dialy Bull 7:138, 1987





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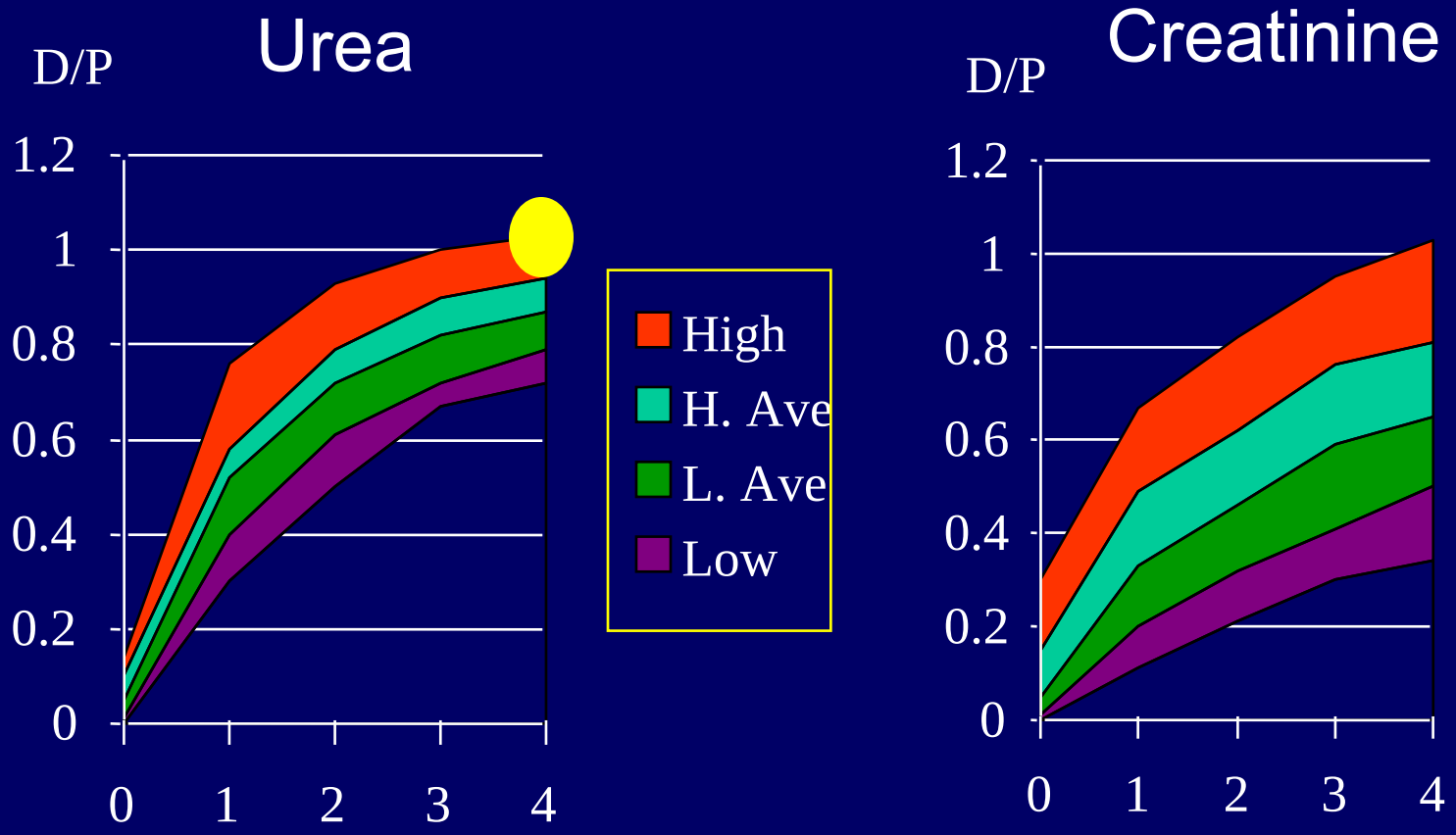
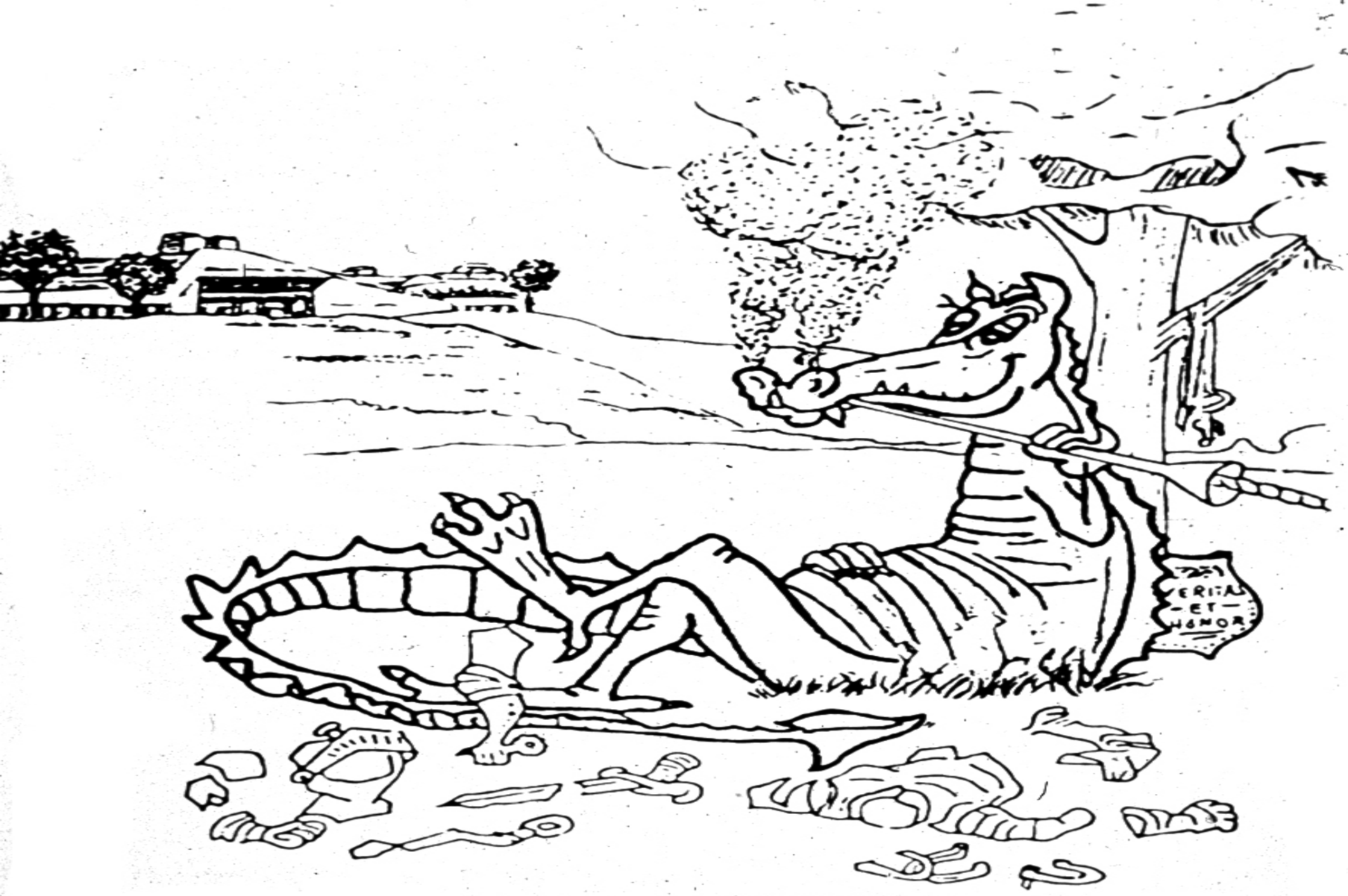


A Very Aggressive Approach

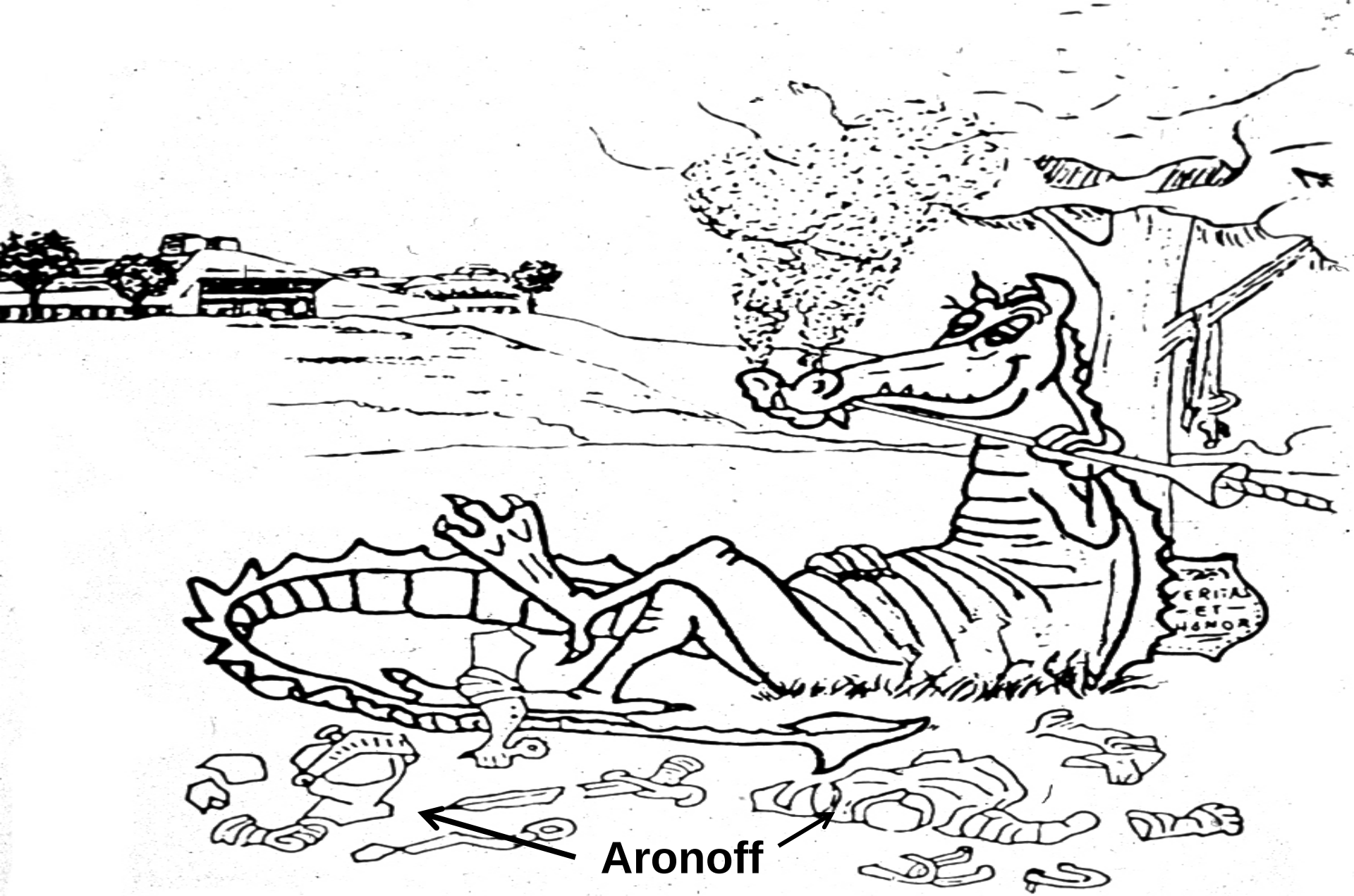
- Assume an exchange every 4 hours of 2.5 liters, fully saturated with urea plus another 250 mL of ultrafiltrate for an effluent volume of 2750 mL fully saturated with urea (liberal assumptions)
- Urea clearance is 2750 mL in 240 minutes or 11.5 mL/min
- Almost all Urea clearance calculations will yield values < 15 mL/min

Conclusions

- As far as drugs are concerned, all will have a clearance < than that of urea, except perhaps lithium
- Drug clearance by typical PD will be about 10 mL/min



Sometimes the Dragon Wins...



Sometimes the Dragon Wins...

Use of the Peritoneal Membrane for Drug Administration

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Intraperitoneal Drug Administration

Option in acute/chronic PD patients

Potential advantages:

- High local / regional concentrations
- Rapid administration
  without need for venous access
- Continuous administration possible
- Avoidance of painful subcutaneous injections

Intraperitoneal Drug Administration

Prerequisites for intraperitoneal applicability:

- Drug solubility and stability in PD fluid

Determinants of systemic resorption:

- Dialysate to plasma concentration gradient
- Molecular size and electrochemical properties
- Exposure time
- Dialysate volume (dilution factor)
- Peritoneal perfusion rate (effective surface area)

Intraperitoneal Drug Administration

Ample experience:

- Local heparin
- Antibiotics
- Chemotherapeutic agents

Limited experience:

- Calcitriol
- Insulin
- Epoietin
- Growth hormone

Recommended IP Antibiotic Dosing in CAPD

Intraperitoneal Antibiotic Dosing Recommendations for CAPD Patients. 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%

	Intermittent (per exchange, once daily)	Continuous (mg/L, all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin	0.6 mg/kg	LD 8, MD 4
Netilmicin	0.6 mg/kg	LD 8, MD 4
Tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin	15 mg/kg	LD 500, MD 125
Cefepime	1 g	LD 500, MD 125
Cephalothin	15 mg/kg	LD 500, MD 125
Cephradine	15 mg/kg	LD 500, MD 125
Ceftazidime	1000–1500 mg	LD 500, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Penicillins		
Azlocillin	ND	LD 500, MD 250
Ampicillin	ND	MD 125
Oxacillin	ND	MD 125
Nafcillin	ND	MD 125
Amoxicillin	ND	LD 250–500, MD 50
Penicillin G	ND	LD 50000 units, MD 25000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Vancomycin	15–30 mg/kg every 5–7 days	LD 1000, MD 25
Aztreonam	ND	LD 1000, MD 250
Antifungals		
Amphotericin	NA	1.5
Combinations		
Ampicillin/sulbactam	2 g every 12 hours	LD 1000, MD 100
Imipenem/cilistatin	1 g b.i.d.	LD 500, MD 200
Quinupristin/dalfopristin	25 mg/L in alternate bags[a]	

Piraino et al. PDI 2005; 25: 436-440107-31

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

HAROLD J. MANLEY,* GEORGE R. BAILIE,*† REGINALD FRYE,§ LORRAINE D. HESS,‡ and M. DONALD MCGOLDRICK†

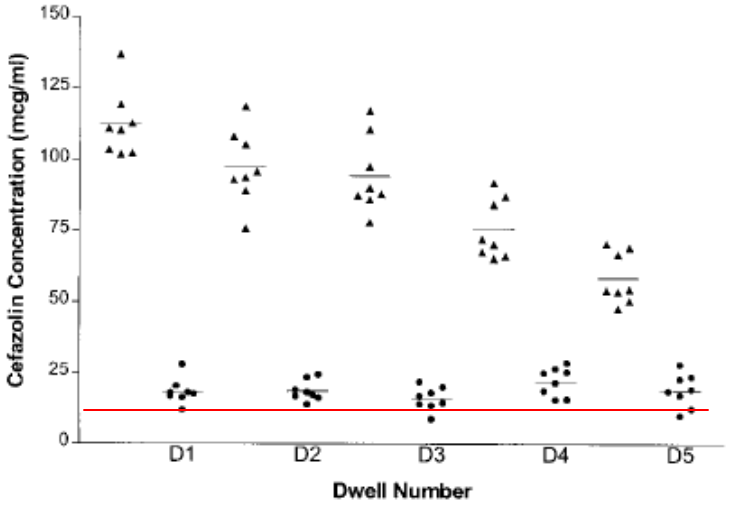
J Am Soc Nephrol 11: 1310–1316, 2000

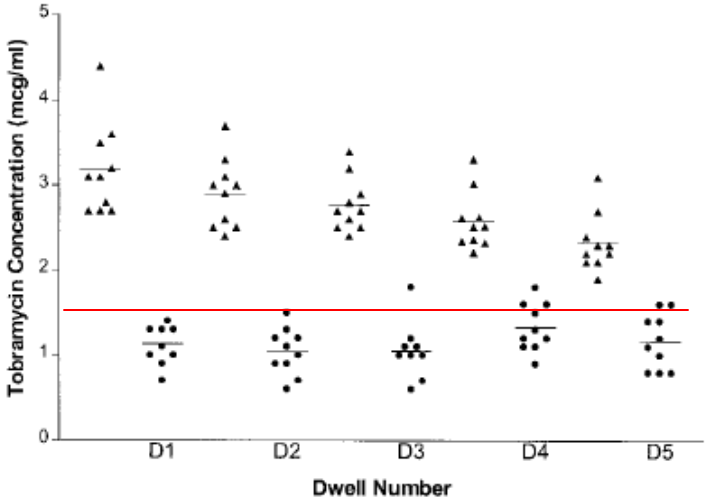
Intravenous loading: 15 mg/kg cefazolin & 0.6 mg/kg tobramycin

APD / CAPD simulation:
3 2.5h, followed by 2 8h exchanges

$t_{1/2}$ 3 short dwells:
Cefazolin 10.7 h, tobramycin 23.1 h

$t_{1/2}$ 2 long dwells:
Cefazolin 14.3 h, tobramycin 68.5 h





INFLUENCE OF PERITONEAL DIALYSATE FLOW RATE ON THE PHARMACOKINETICS OF CEFAZOLIN

Harold J. Manley,[1,2] Darcie L. Bridwell,[1,3] Rowland J. Elwell,[4] and George R. Bailie[4,5]

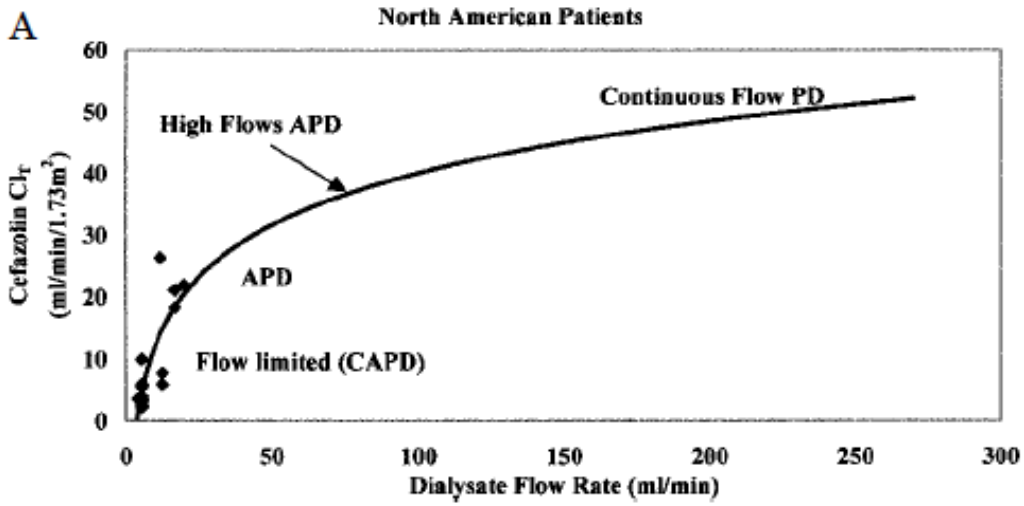
Perit Dial Int 2003; 23:469–474

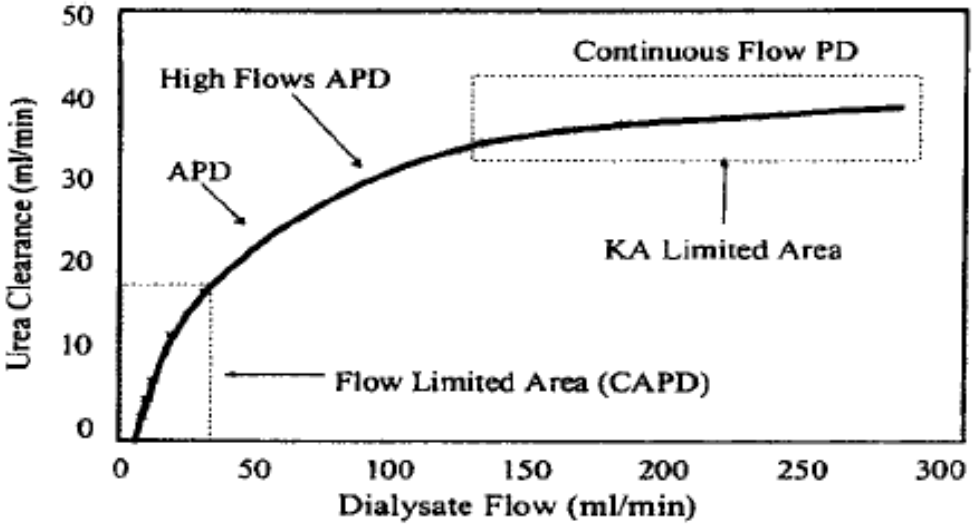
Meta-analysis of 55 patients investigated in 5 studies

Mean Patient Demographics and Pharmacokinetic Parameters

	Reported (n)	Mean±SD
Pharmacokinetic parameters		
k_{el}	41	0.037±0.025/hour
t1/2	53	27.11±14.77 hours
Cl_{PD}	53	1.55±1.27 mL/min/1.73 m^2
Cl_T	20	6.96±6.47 mL/min/1.73 m^2
DFR	54	7.04±3.90 mL/min
Vd	54	0.22±0.17 L/kg
$t1/2_{PD}$	35	2.51±1.08 hours
F	33	76.7%±8.79%

PK parameter	DFR > 5.50 mL/minute	DFR ≤ 5.50 mL/minute	p Value
DFR	13.76±2.54	4.97±0.67	<0.0001
k_{el} (/hour)	0.063±0.031	0.027±0.009	<0.0001
t1/2 (hours)	13.73±6.50	27.56±10.66	<0.0001
$t1/2_{PD}$ (hours)	1.53±0.57	3.18±0.87	<0.0001
Cl_T (mL/min/1.73 m^2)	16.89±8.23	4.33±1.97	<0.0001
Cl_{PD} (mL/min/1.73 m^2)	1.54±0.54	1.08±0.73	0.036

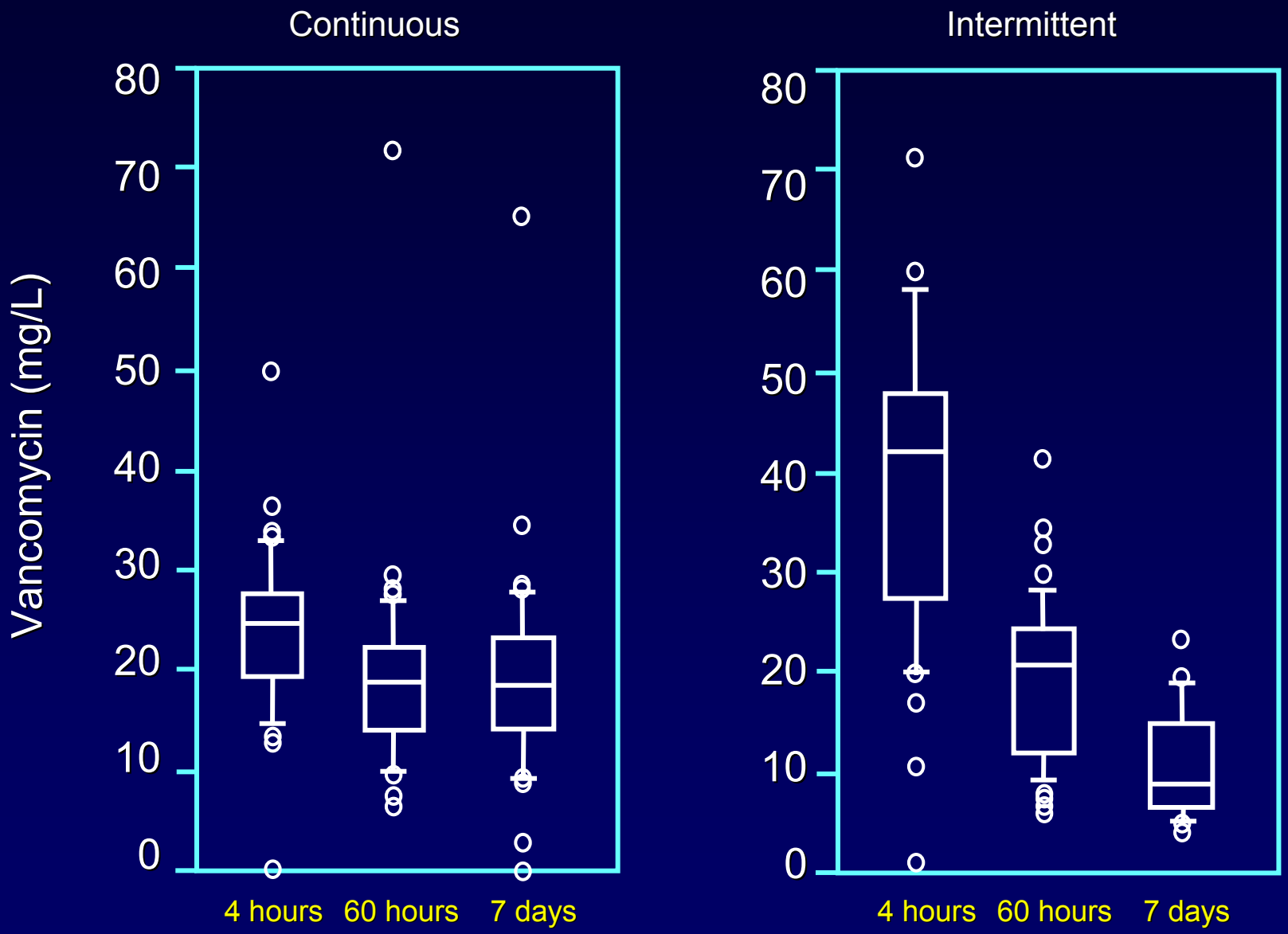




Urea clearance versus dialysate flow rate.

Perit Dial Int 2003; 23:469–474

Continuous vs. Intermittent IP Gycopeptides in Children with PD-Associated Peritonitis



Schaefer et al. J Am Soc Nephrol 1999

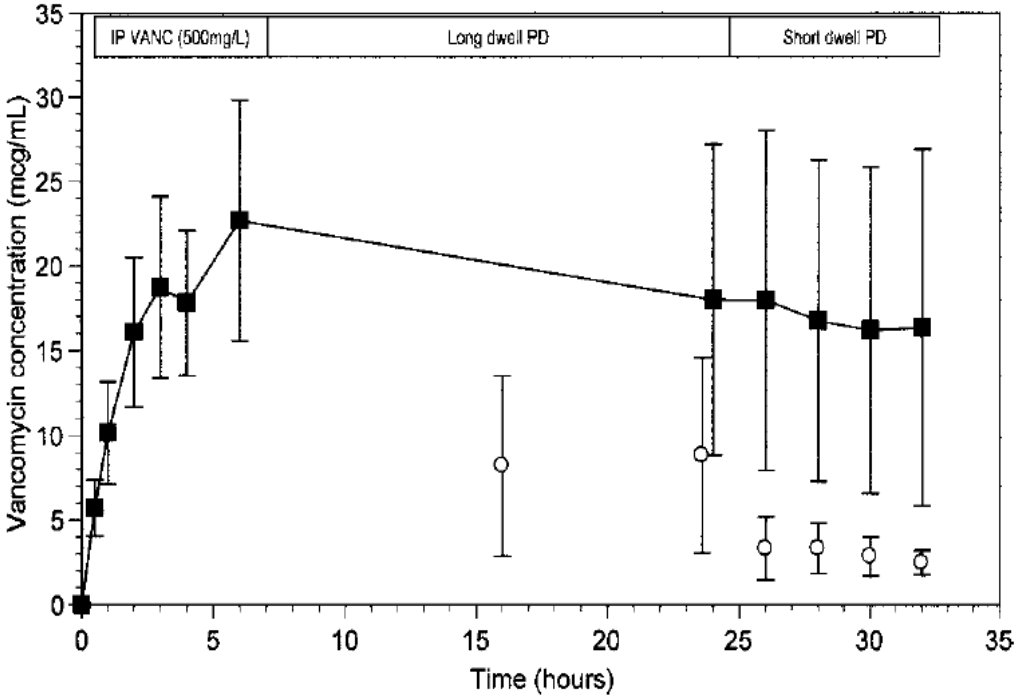
Vancomycin Pharmacokinetics in Children

6-hour IP administration vancomycin 500 mg/L

Bioavailability: 70%

90 min D/P vancomycin: 0.22 ± 0.11

Non-dialytic, extrarenal vancomycin clearance higher than in adults !



Patient	% Absorbed (F)	6-hour level (µg/mL)	Vd (L/kg)	λz (L/hour)	t½ (hours)	Clearance (mL/minute/1.73 m²) Total	Renal	CAPD	APD
1	0.75	20.2	0.41	0.0205	33.8	11.04	0	4.07	5.01
2	0.71	31.6	0.76	0.0331	21.0	10.59	0.63	2.45	4.03
3	0.68	16.0	0.71	0.0294	23.5	16.17	8.38	3.35	3.16
4	0.65	31.8	0.22	0.0255	27.1	4.99	0	0.88	2.18
5	0.62	28.5	0.23	0.0263	26.4	4.54	0	2.24	1.56
6	0.77	20.0	0.37	0.0321	21.6	12.83	0.64	1.71	1.88
7	0.68	15.0	0.70	0.0318	21.8	14.90	0	2.52	3.85
Mean±SD	0.7±0.05	23.3±7.2	0.48±0.24	0.0284±0.0045	25.0±4.6	10.72±4.52	1.38±3.10	2.46±1.04	3.09±1.28

Blowey et al. PDI 2007

Recommended Intermittent Vancomycin Dosing in Children

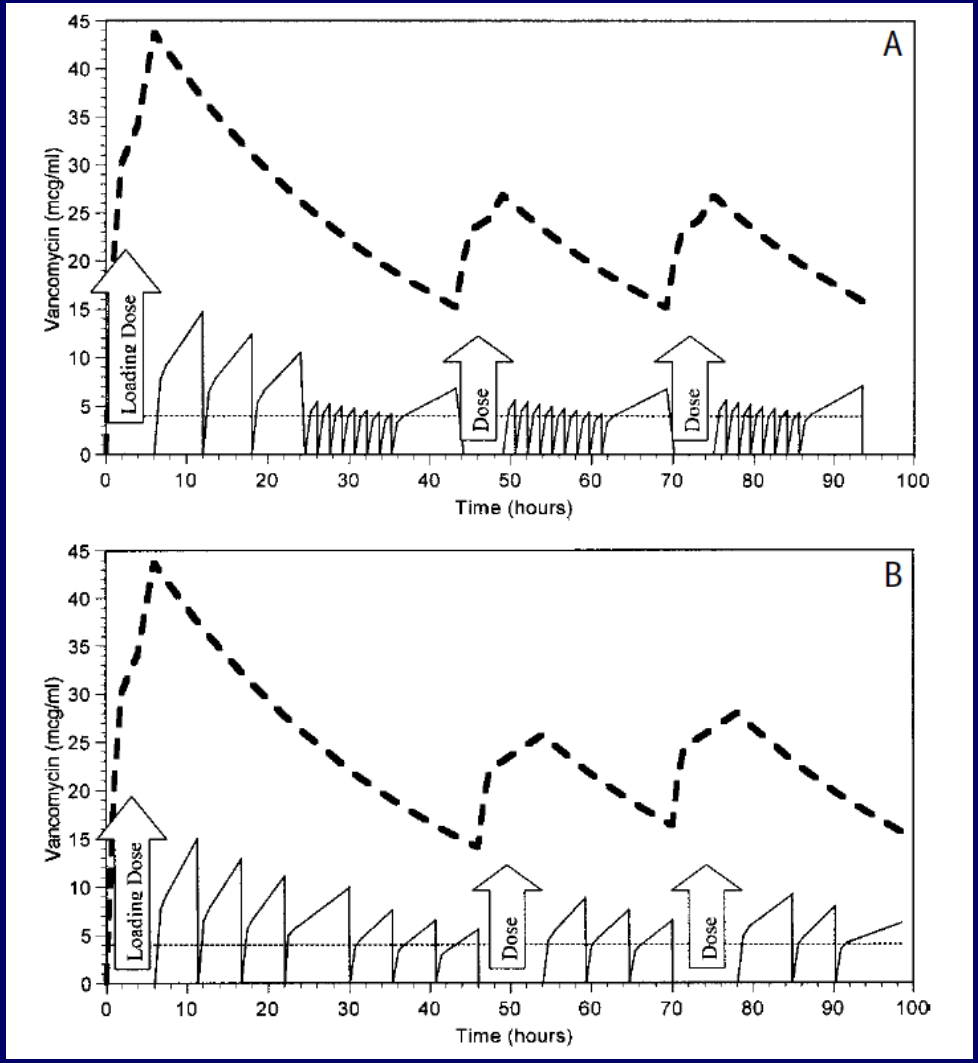
Serum vancomycin level required to achieve effluent level > MIC:
18 mg/ml for APD,
9 mg/ml for CAPD regimens

Recommended intermittent dosing in pediatrics:

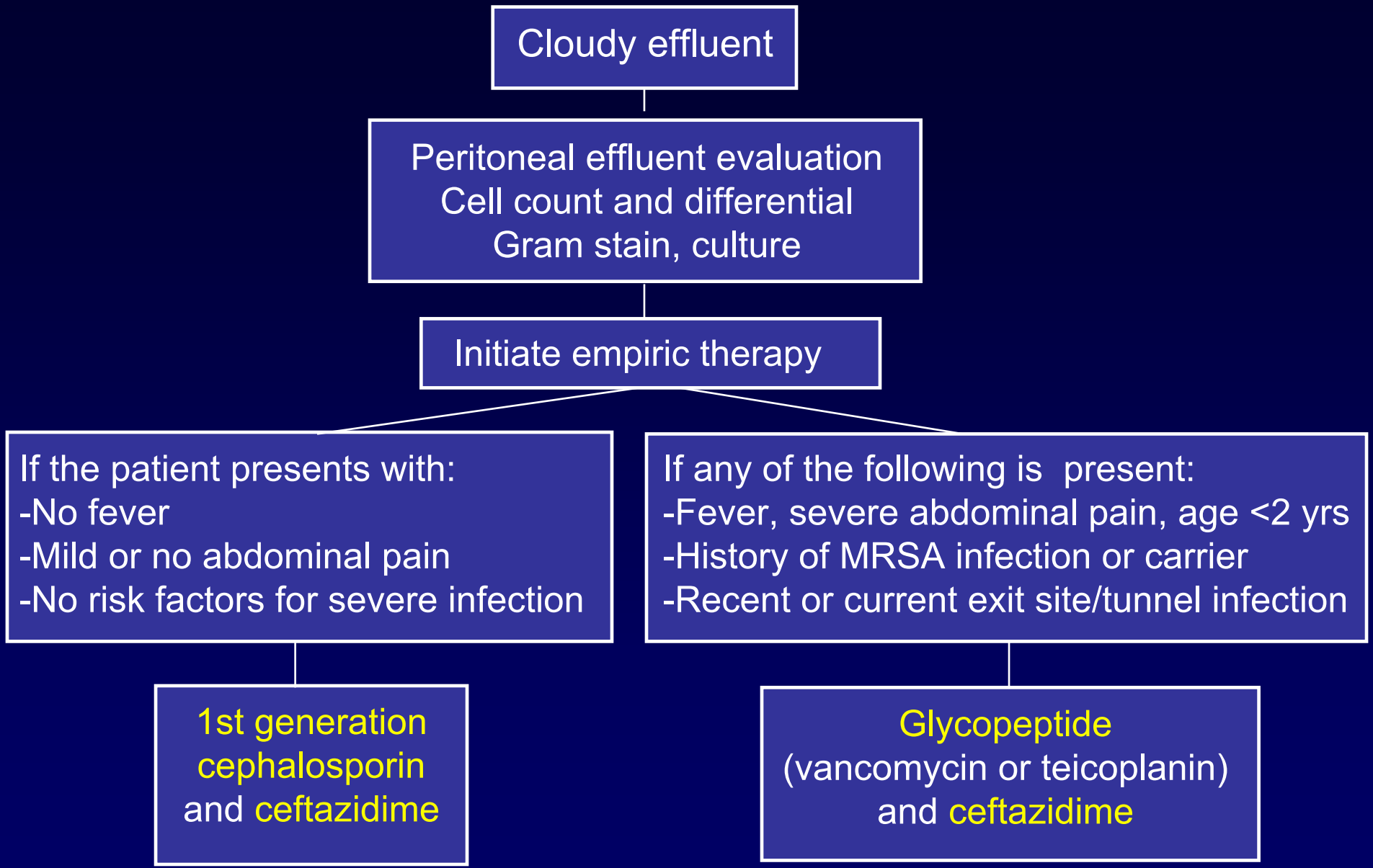
LD 30 mg/kg

ED 7.5 mg/kg daily starting on day 3

Monitor trough blood levels day 3/4



Blowey et al. PDI 2007; 27: 79-85



ISPD Pediatric Guidelines, PDI 2000

Clinical Response Failure after 72h Empiric Antibiotic Treatment

	Cefazolin/ Ceftazidime	Glycopeptide/ Ceftazidime	Any Treatment
Gram positive	5/90 (5.6%)	4/129 (3.1%)	9/219 (4.1%)
Gram negative	4/56 (7.1%)	12/65 (18.5%)	16/121 (13.2%)*
Culture negative	4/92 (4.4%)	2/59 (3.4%)	6/151 (4.0%)
Any culture result	13/238 (5.5%)	18/253 (7.1%)	31/491 (6.3%)

Warady et al. for IPPR, JASN 2007; 18:2172

Risk of Day 3 Clinical Response Failure

	Odds ratio (95% CI)	P
Gram-negative causative organism	3.61 (1.73 - 7.54)	P <0.001
Intermittent ceftazidime administration (only gram-negative)	6.65 (2.07 – 21.4)	P <0.005
APD modality: 'dry day' vs. 'wet day'	2.53 (1.18 - 5.42)	P <0.01
Exit site score >2 (only gram-positive)	5.46 (1.02 - 29.7)	P <0.05

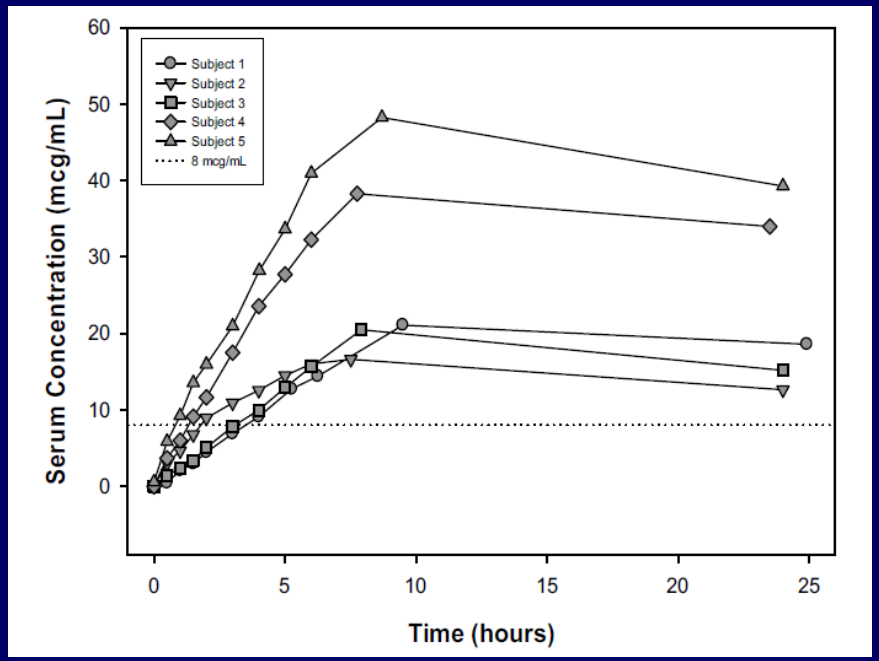
Warady et al. for IPPR, JASN 2007; 18:2172

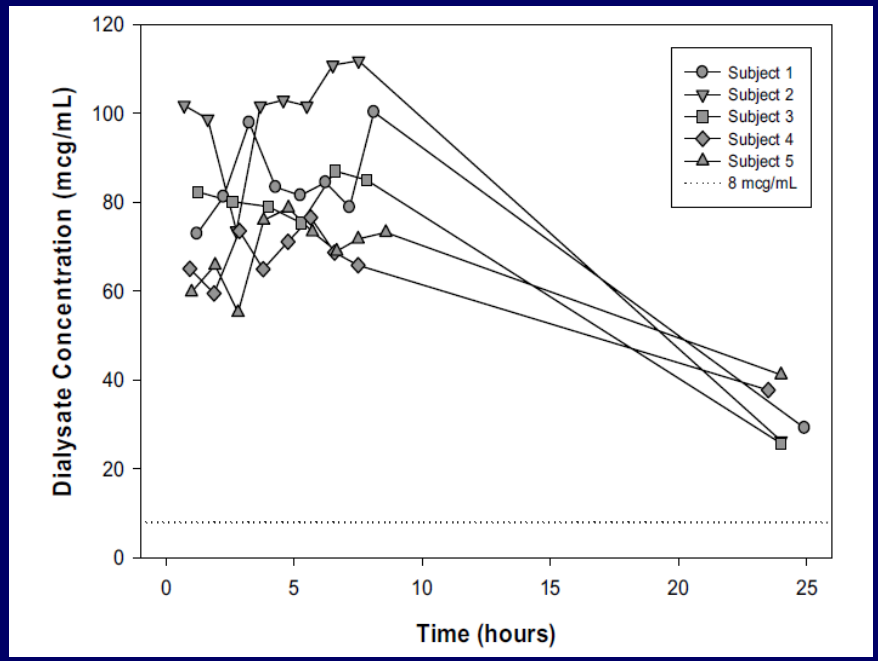
Disposition of Ceftazidime After Intraperitoneal Administration in Adolescent Patients Receiving Continuous Cycling Peritoneal Dialysis

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

Maintenance dose applied without loading dose during 10-hour NIPD:

Serum level exceeding MIC within <4 hours,
dialysate levels >> MIC for 24 hours





AJKD 2006; 47: 503-8

IP Administration of Vit D Analogues (MW: 416 Da)

- Rapid resorption (within 90 min) from peritoneal cavity
- Variable adsorption to PD bags (Calcitriol: 25% in 4 hrs)
- PTH suppressive efficacy (calcitriol): IV > IP ≥ PO

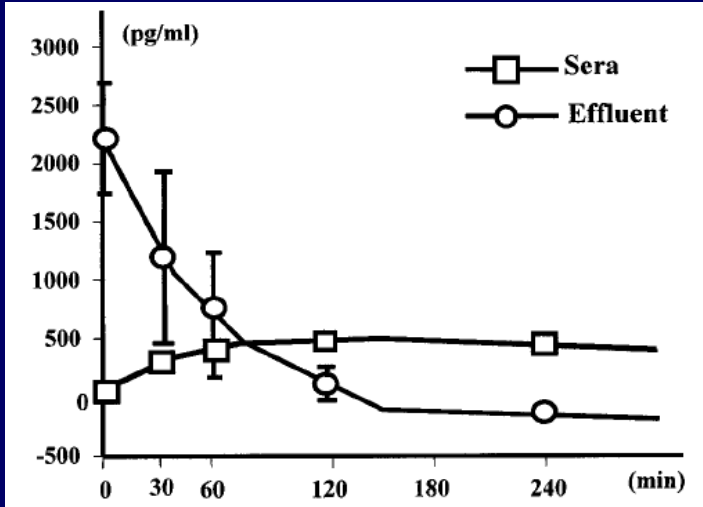
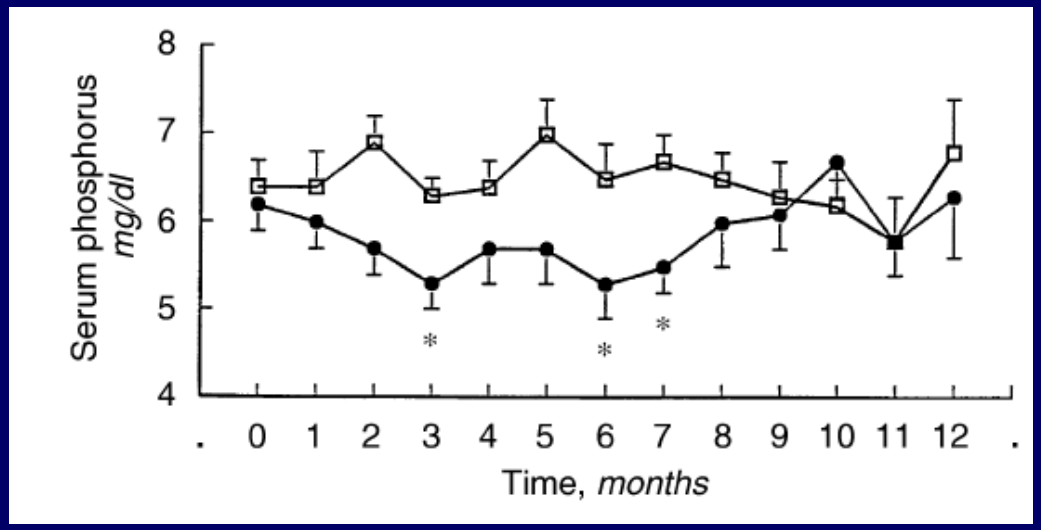
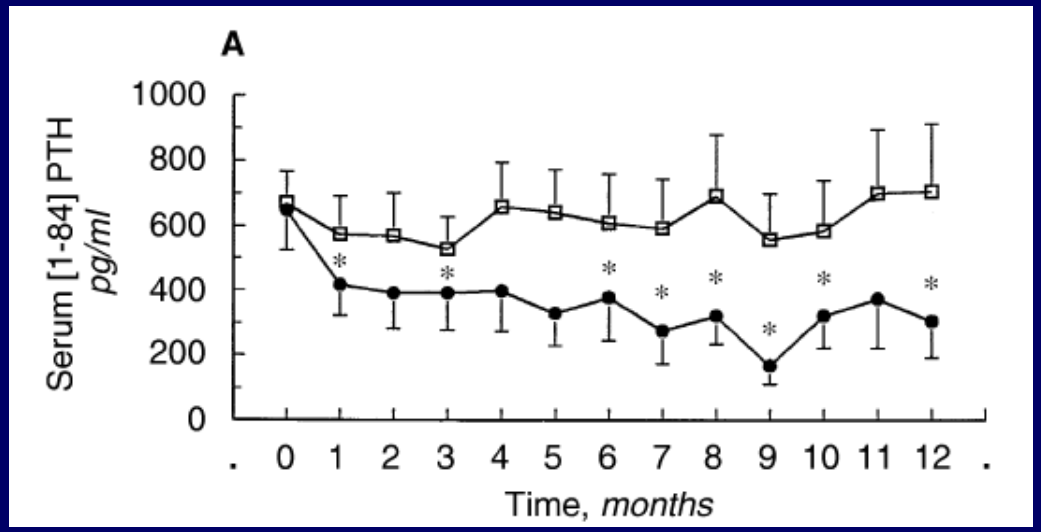


Figure 4 — Time-course changes of maxacalcitol (OCT) activity in serum (open squares) and effluent (open circles) were determined at 0, 60, 120, and 240 minutes after a single intraperitoneal dose of OCT (10 μg).

Delmez et al. KI 1987, Chan et al. PDI 1998, Salusky et al. KI 1998
Hamada et al. PDI 2005, Cano et al. PDI 2007

IP vs. Oral Calcitriol Pulse Therapy





Salusky et al. KI 1998; 54: 907-14

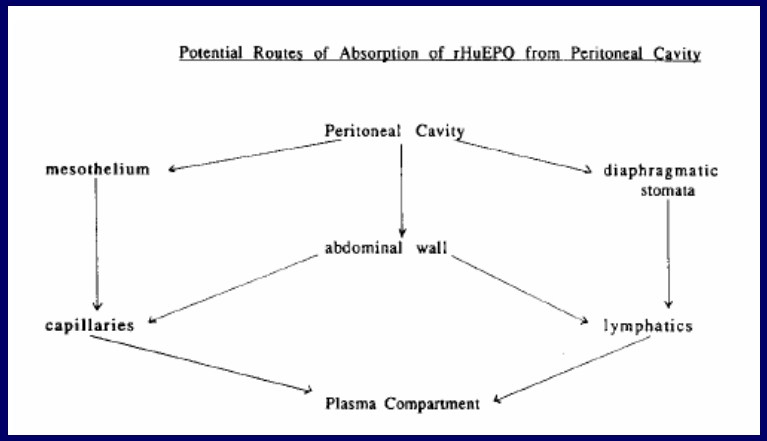
IP Insulin Administration (MW: 6 kD)

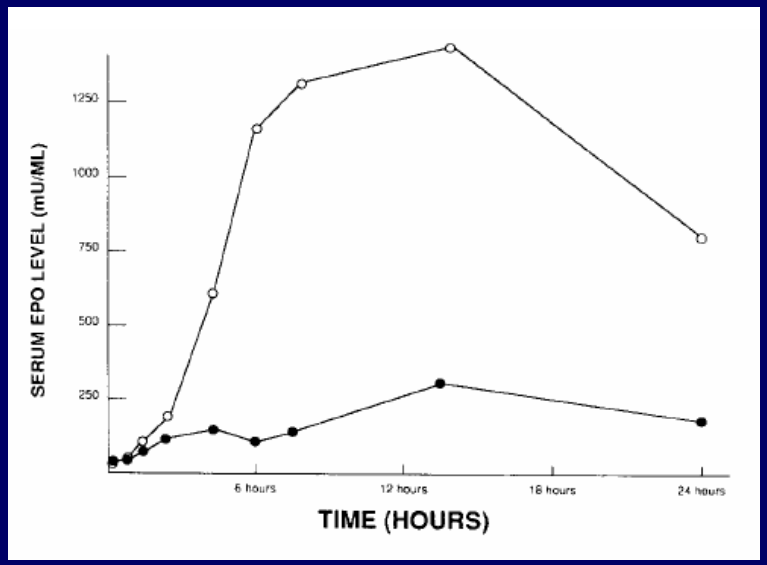
- Good resorption from peritoneal cavity with 3-4 hour dwells
- 20-65% adsorption to PD bags
- More physiological insulin action by portal uptake?
  More stable blood glucose profile by steady insulin resorption ?
- Equivalent or superior blood glucose control
- IP insulin dose requirements simular or reduced vs SC
  if administered into empty peritoneal cavity
- Hypoglycemic episodes less frequent
- Dyslipidemia more marked
- Anecdotal subcapsular hepatic steatosis
- Stimulation of peritoneal neoangiogenesis ??

IP Administration of Epoietin (MW 34 kD)

- Little adsorption to PD bags (<7%)
- Lymphatic drainage presumed main route of resorption
- Bioavailability strongly determined by dilution and exposure time

  -> Prolonged instillation of concentrated protein required
  -> NIPD regimen most suitable
- IP preferred by patients for avoidance of injection pain

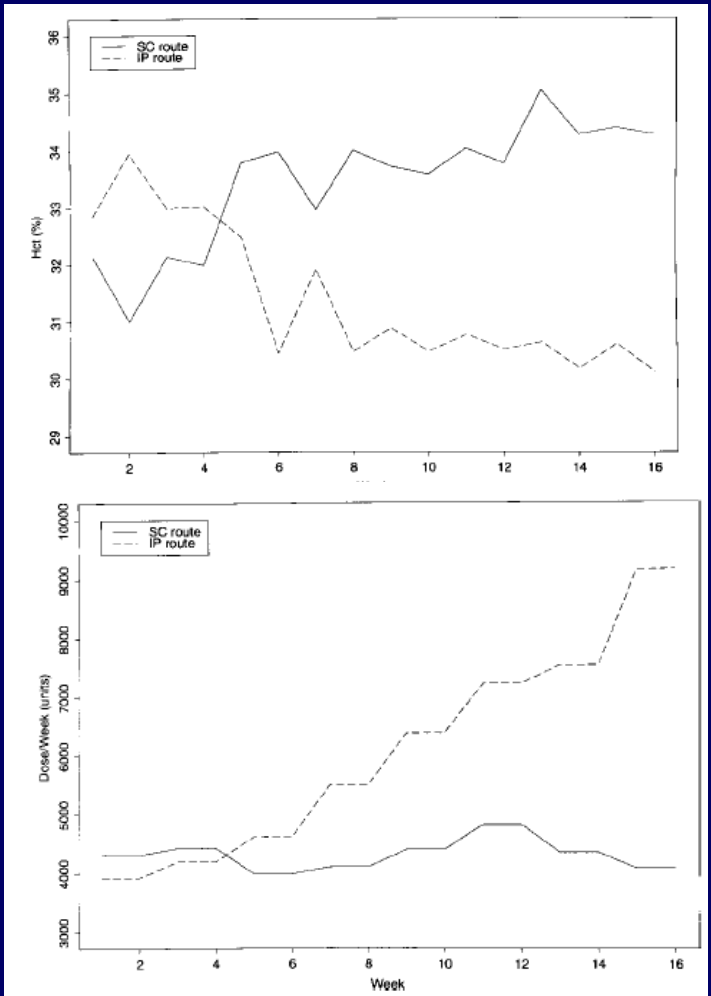




Bargman et al. PDI 1993

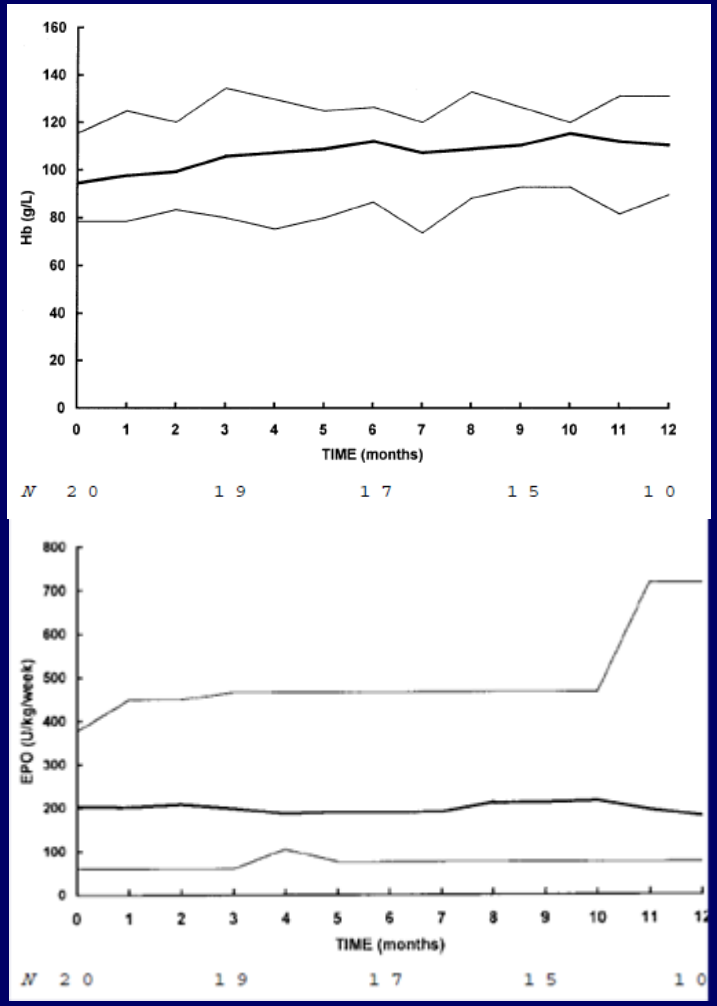
IP Administration of Epoietin-alpha

Adult CAPD: EPO in empty cavity with 30 ml NaCl flush, 8h dwell time; once weekly dosing



Johnson et al. PDI 1999; 19: 578-82

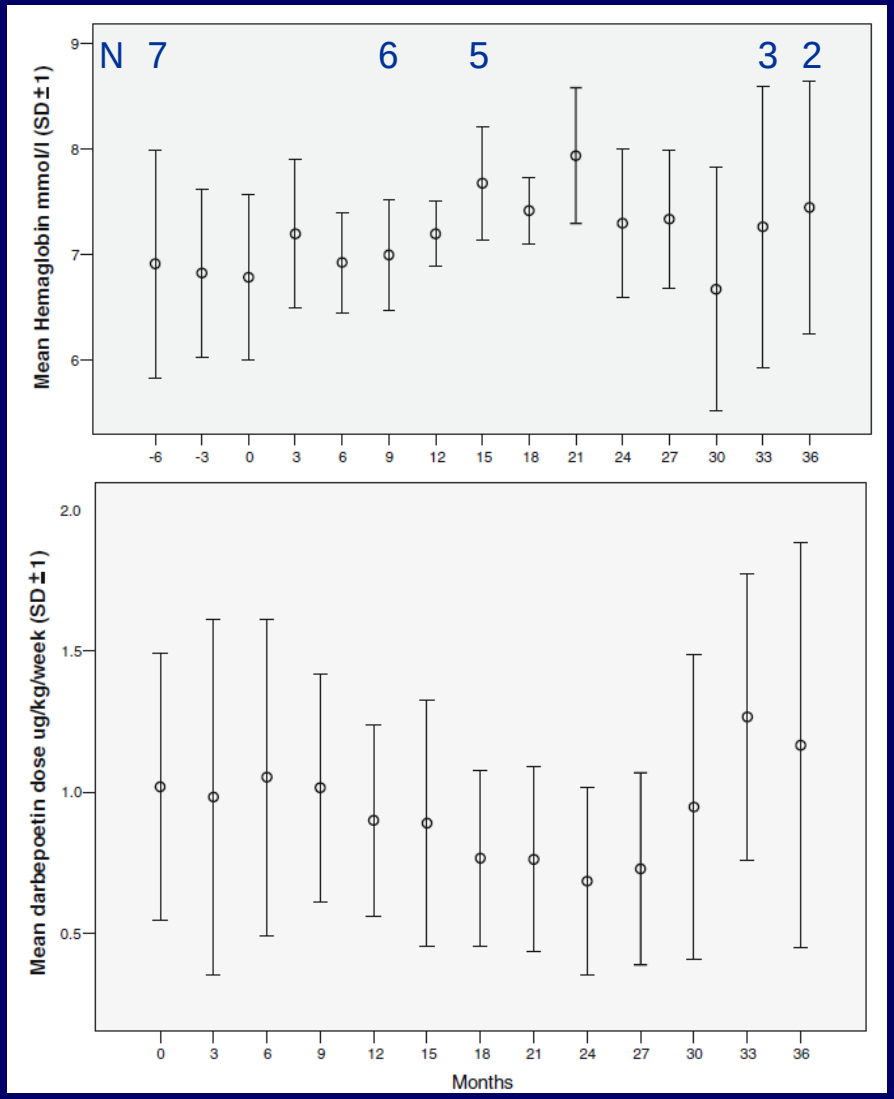
Pediatric NIPD: EPO instillation via 50 ml NaCl bags, 10-12h dwell time; once weekly dosing



Rusthoven et al. PDI 2001; 21: 193-7

IP Administration of Darbepoietin

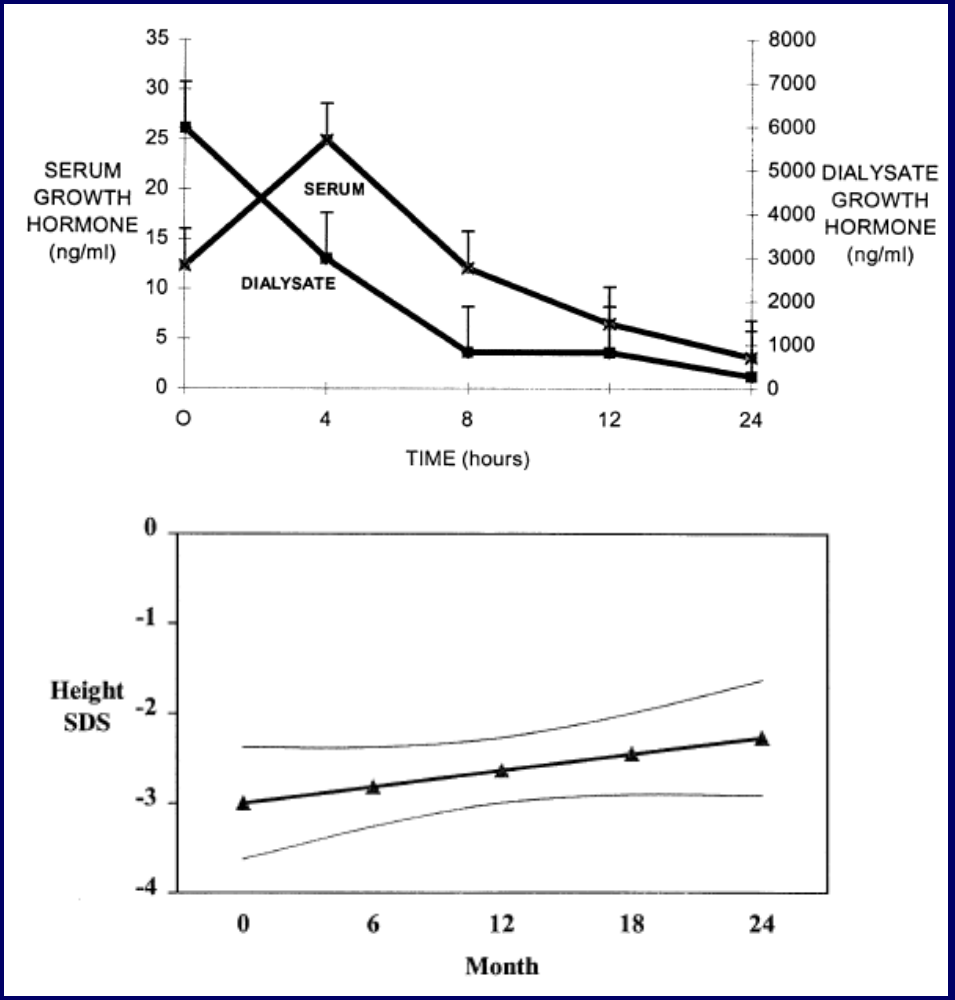
Children with NIPD
Once weekly
10-12h dwell time
1:1 dose switch from s.c.



Rijk et al. Pediatr Nephrol 2007; 22: 436-440

IP Administration of Recombinant Growth Hormone (MW: 18 kD)

- Adherence to PD materials <7%
- Bioavailability similar to SC route (85% by 8h exposure)
- Peak serum level after 4h
- Serum half-life 4.6 h
- Growth stimulation comparable to SC dosing



Gipson et al. Pediatr Nephrol 2001; 16:29-34

Conclusions

- IP route: interesting option to adminster drugs in PD patients
- IP first-line mode of parenteral antibiotic administration
- Molecular size and exposure time main determinants of IP bioavailability
- PK/PD studies, effect modeling of modifications in PD schedule required
- Consider practical pro's and con's