The Physiology of Peritoneal Dialysis As Related To Drug Removal

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Clearance By Dialysis

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

or

D/P times effluent vol/time
Diffusion Curves

Dialysate to Plasma (D/P) concentration ratios

- Urea
- Creatinine
- MM

Equilibration; dialysate saturation

Fastest diffusion rate

Dwell time (hours)
Peritoneal Equilibration Test

Urea

Creatinine

D/P
D/P

High
H. Ave
L. Ave
Low
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

Dissociation Between Clearance of Small and Middle Molecular Weight Toxins

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

D/P Creatinine

Total Dialysate V

CrCL/exchange

High Transporter

Low Transporter
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

The diagram illustrates the relationship between molecular weight (daltons) and clearance (ml/min) for different dwell times (1 hour, 4 hours, 8 hours) in the context of dialysis. The graph shows a decreasing trend in clearance as molecular weight increases, with distinct lines for each dwell time. The y-axis represents clearance in ml/min, while the x-axis represents molecular weight in daltons. The ratio $C_x/C_{urea}$ is also plotted on the right y-axis.
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)

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

\[
K = 7.3 \text{ mL/min}
\]
Peritoneal Equilibration Test

Urea

Creatinine

D/P

D/P

0 1 2 3 4

0 1 2 3 4

High
H. Ave
L. Ave
Low
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%

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

Piraino et al. PDI 2005; 25: 436-440107-31
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. Bailie4,5

Meta-analysis of 55 patients investigated in 5 studies

<table>
<thead>
<tr>
<th>Mean Patient Demographics and Pharmacokinetic Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported (n)</td>
</tr>
<tr>
<td>Pharmacokinetic parameters</td>
</tr>
<tr>
<td>$k_{el}$</td>
</tr>
<tr>
<td>$t1/2$</td>
</tr>
<tr>
<td>$Cl_{PD}$</td>
</tr>
<tr>
<td>$Cl_T$</td>
</tr>
<tr>
<td>DFR</td>
</tr>
<tr>
<td>Vd</td>
</tr>
<tr>
<td>$t1/2_{PD}$</td>
</tr>
<tr>
<td>F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>DFR &gt; 5.50 mL/minute</th>
<th>DFR ≦ 5.50 mL/minute</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFR</td>
<td>13.76±2.54</td>
<td>4.97±0.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$k_{el}$ (hour)</td>
<td>0.063±0.031</td>
<td>0.027±0.009</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$t1/2$ (hours)</td>
<td>13.73±6.50</td>
<td>27.56±10.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$t1/2_{PD}$ (hours)</td>
<td>1.53±0.57</td>
<td>3.18±0.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$Cl_T$ (mL/min/1.73 m²)</td>
<td>16.89±8.23</td>
<td>4.33±1.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$Cl_{PD}$ (mL/min/1.73 m²)</td>
<td>1.54±0.54</td>
<td>1.08±0.73</td>
<td>0.036</td>
</tr>
</tbody>
</table>
Urea clearance versus dialysate flow rate.

Perit Dial Int 2003; 23:469-474
Continuous vs. Intermittent IP Gycopeptides in Children with PD-Associated Peritonitis

Vancomycin (mg/L)

Continuous vs. Intermittent in Children with PD-Associated Peritonitis

Vancomycin (mg/L)

Continuous vs. Intermittent in Children with PD-Associated Peritonitis

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!

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
If the patient presents with:
- No fever
- Mild or no abdominal pain
- No risk factors for severe infection

Glycopeptide (vancomycin or teicoplanin) and ceftazidime

If any of the following is present:
- Fever, severe abdominal pain, age <2 yrs
- History of MRSA infection or carrier
- Recent or current exit site/tunnel infection

Initiate empiric therapy

Peritoneal effluent evaluation
- Cell count and differential
- Gram stain, culture

1st generation cephalosporin and ceftazidime

ISPD Pediatric Guidelines, PDI 2000
## Clinical Response Failure after 72h Empiric Antibiotic Treatment

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

Warady et al. for IPPR, JASN 2007; 18:2172
## Risk of Day 3 Clinical Response Failure

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative causative organism</td>
<td>3.61 (1.73 - 7.54)</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Intermittent ceftazidime administration (only gram-negative)</td>
<td>6.65 (2.07 – 21.4)</td>
<td>P &lt;0.005</td>
</tr>
<tr>
<td>APD modality: 'dry day' vs. 'wet day'</td>
<td>2.53 (1.18 - 5.42)</td>
<td>P &lt;0.01</td>
</tr>
<tr>
<td>Exit site score &gt;2 (only gram-positive)</td>
<td>5.46 (1.02 - 29.7)</td>
<td>P &lt;0.05</td>
</tr>
</tbody>
</table>

Warady et al. for IPPR, JASN 2007; 18:2172
Maintenance dose applied without loading dose during 10-hour NIPD:

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

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 similar 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

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

Johnson et al. PDI 1999; 19: 578-82
Rusthoven et al. PDI 2001; 21: 193-7
Children with NIPD
Once weekly
10-12h dwell time
1:1 dose switch from s.c.

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

Conclusions

- IP route: interesting option to administer 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