Peritoneal Dialysis

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My Deets

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Disclosures

- DaVita Healthcare: Speaker and Consultant
- Baxter Canada: Speaker and Consultant
- Baxter Global: Speaker
- GSK: Consultant
- Novartis: Consultant
Objectives

We will discuss patient cases to illustrate the following:

- **Peritoneal transport**
  - solute flux
  - ultrafiltration
- **Peritoneal dialysis solutions**
  - dextrose-based
  - icodextrin
- **Adequacy of PD**
- **Approach to volume management**
The “Rapid Transporter” – so what?

• 67 year old woman with type II diabetes starts on peritoneal dialysis

• two months later, peritoneal equilibration test (PET) shows that the D/P creatinine at 4 hours is 0.90 (“high” or “rapid” transporter)
Which ONE of the following statements about D/P creatinine is TRUE?

A. The D/P creatinine is an important predictor of dialysis adequacy.
B. The PET test was performed too soon after the start of PD.
C. There may be problems with ultrafiltration, especially during the long dwell of dialysate.
D. Icodextrin is not useful for this high or rapid transporter
How PD Works: The Peritoneal-Vascular Interface

capillaries

Peritoneal membrane

Peritoneal cavity
How PD Works: The Peritoneal-Vascular Interface

- Peritoneal membrane
- Peritoneal cavity
- Capillaries
The Peritoneal-Vascular Interface

Blood side

endothelial cells

interstitium

Dialysate side (peritoneal cavity)

mesothelial cells

peritoneal membrane
The Peritoneal-Vascular Interface

Regulation of transport occurs here.

- Blood side
  - endothelial cells
  - interstitium

- Dialysate side
  - mesothelial cells
  - peritoneal membrane

(peritoneal cavity)
Solute Transport in PD: How Does Solute Get from the Blood to the Peritoneal Fluid?

I. Diffusion

II. Convection (during ultrafiltration)
Diffusion Kinetics - from blood to dialysate

- diffusive flux is fastest in the first hour and slows over time
- by 4 hours, urea is > 90% equilibrated, creatinine about 60% equilibrated
- further small solute removal is minimal after that
- long dwells more important for removal of middle and larger MW solutes
Diffusion Curves – a Schema

Dwell time (hours)

Dialysate-to-plasma (D/P) ratios

- urea
- creatinine
- middle molecules (time-dependent)
Diffusion Kinetics - *from dialysate to blood*

**What can you add to dialysate?**

- antibiotics (not just for peritonitis)
- insulin
- KCl (up to 10 mEq/l)
- xylocaine, NaHCO₃ (infusion pain)
- erythropoietin
Ultrafiltration in PD

• result of osmotic pressure (compared to HD where produced by hydraulic pressure)

• results of ultrafiltration:
  – fluid removal
  – convective removal of solutes, especially middle molecules
Composition of Peritoneal Dialysate: Osmolality

- 1.5% dextrose - 347 mOsm/l (isotonic)
- 2.5% dextrose - 397 mOsm/l (hypertonic)
- 4.25% dextrose - 485 mOsm/l (more hypertonic)
Ultrafiltration in Peritoneal Dialysis

Example: 4.25% dextrose dialysate
Ultrafiltration: 4.25% Dialysate

Water will move from lower to higher osmolality

320 mOsm | 480 mOsm
---|---
blood | peritoneal cavity
Ultrafiltration: 4.25% Dialysate

*Water will move from lower to higher osmolality and take solute with it*
Ultrafiltration in PD: The Bad News

The glucose itself diffuses out of peritoneal cavity along its own concentration gradient

100 mg/dl  3,860 mg/dl

blood  peritoneal cavity
Ultrafiltration in PD is Time-Dependent

- Ultrafiltration volume
- Osmotic equilibrium
- Net reabsorption

Time (hours)
Typical Ultrafiltration Values in PD

1.5 % Dialysate
- maximum UF 330 +/- 187 ml
- time to maximum UF 140 +/- 48 minutes

4.25 % Dialysate
- maximum UF 1028 +/- 258 ml
- time to maximum UF 247 +/- 61 minutes
Snap Quiz

• a 4.25% solution typically leads to 1L of UF over 4h (=250 ml/hr)
• why are PD patients switched to HD for fluid removal if they end up in ICU?

Beats me…
Typical Ultrafiltration Curves for Each Strength of Dialysate

Summary of Ultrafiltration in PD

The amount of UF depends upon:

- *tonicity* of dialysate
  - 4.25% > 2.5% > 1.5%
- *duration* of dialysate dwell
  - after osmotic equilibration, fluid starts to be absorbed
- *permeability* of peritoneal membrane to glucose
  - osmotic gradient dissipates faster across a more permeable membrane
The Peritoneal Equilibration Test (PET): A Way to Characterize the Peritoneal Membrane

At time $t = 0$: 

- Blood (creatinine)
- Peritoneal cavity (glucose)
The Peritoneal Equilibration Test (PET): A Way to Characterize the Peritoneal Membrane

Solute diffusion along their concentration gradient:

- Blood (creatinine)
- Peritoneal cavity (glucose)
The Peritoneal Equilibration Test

How easily does creatinine cross from blood to the peritoneal cavity?

- quantified as Dialysate [creatinine]
  Plasma [creatinine]
  or
  D/P creatinine (at T = 4 hours)
- the “leakier” the peritoneal membrane, the higher the D/P creatinine
The Peritoneal Equilibration Test (PET): A Way to Characterize the Peritoneal Membrane

“leaky” peritoneal membrane
(rapid transporter)
The Peritoneal Equilibration Test (PET): A Way to Characterize the Peritoneal Membrane

“tight” peritoneal membrane
(slow transporter)

Lower D/P Creatinine

Lower D/P Glucose

blood

Peritoneal cavity

(creatine)

(glucose)
Peritoneal Equilibration Test

D/P Urea

D/P Creatinine

Twardowski et al. Perit Dial Bull
Membrane Permeability and Ultrafiltration - “rapid transporters”

the “leakier” the peritoneal membrane (more vascular beds are open)

the faster the glucose will diffuse out of the peritoneal cavity

the faster the osmotic gradient will dissipate
Why Is Someone a Rapid Transporter from the Start?

- association with higher CRP, lower serum albumin, less residual renal function
- in some studies, more common in diabetics
- lower serum albumin is seen even before the start of PD

This suggests that rapid transporter status may be a marker of inflammation
Membrane Permeability and Ultrafiltration - *slow transporters*

the “tighter” the peritoneal membrane (fewer open vascular beds)

\[ \downarrow \]

the slower glucose will diffuse out of the peritoneal cavity

\[ \downarrow \]

the osmotic gradient will be maintained longer
Membrane Transport Status – Implications for Ultrafiltration

Drain Volume
(2000 ml infused)

Creatinine

D/P

ml

0
500
1000
1500
2000
2500
3000
3500

slow
Lo Ave
Hi Ave
Rapid

0
0.2
0.4
0.6
0.8
1

0
1
2
3
4
Rapid vs Slow Transporters: Why Solute Removal Isn’t that Different

the better UF in the slow transporters will increase solute removal through convective transport

C=convective flux
D=diffusive flux
Back to Our Patient:

Which ONE of the following statements about our “rapid transporter” is TRUE?

A. The D/P creatinine is an important predictor of dialysis adequacy.
B. The PET test was performed too soon after the start of PD.
C. There may be problems with ultrafiltration, especially during the long dwell of dialysate.
D. Icodextrin is not useful for this high or rapid transporter
• glucose diffuses out of the peritoneal dialysis fluid over time into the systemic circulation
• during a long dwell, the loss of glucose in the dialysis fluid leads to dissipation of the osmotic gradient and ultrafiltration will stop
• this all happens faster in the rapid transporter
Thirsty in the Morning

• A 42 year old woman with IgA nephropathy is on night cycler PD
• The nephrologist wants to impress the administrator and CMS with a high Kt/V urea and prescribes 5 cycles over 9 hours, 2.5% dialysate
• The patient complains of marked thirst in the morning and has to drink several glasses of water
What is the One Best Answer?

A. The sleep apnea syndrome seen in dialysis patients leads to mouth breathing and thirst.
B. The patient may be hypernatremic in the morning because of sodium sieving on PD.
C. The glucose absorption increases the serum osmolality and drives thirst.
D. The morning thirst is the result of resetting of the osmostat because of the cycling PD.
Transport in Peritoneal Dialysis
The Three Pore Model

- Capillary
- Transcellular pore (aquaporin)
- Small pore
- Large pore
- Peritoneal Cavity
- Endothelial cell
Sodium Sieving in Peritoneal Dialysis

1. Water movement through aquaporins

Osmotic gradient

blood

dialysate
Sodium Sieving in Peritoneal Dialysis

2. $\text{Na}^+$ and $\text{H}_2\text{O}$ movement through small pores
Sodium Sieving

- more water than sodium moves into the peritoneal cavity at the beginning of UF
- sodium is held back or “sieved” at the aquaporin
- sodium diffuses into the dialysate more slowly via the intercellular pores
- short dwells will lead to more water than sodium removal
Thirsty in the Morning: Choose the Best Answer

A. The sleep apnea syndrome seen in dialysis patients leads to mouth breathing and thirst.

B. The patient may be hypernatremic in the morning because of sodium sieving on PD.

C. The glucose absorption increases the serum osmolality and drives thirst.

D. The morning thirst is the result of resetting of the osmostat because of the cycling PD.
Aquaporins allow only aqua to cross the endothelial membrane.
Rapid exchanges with hypertonic dialysis fluid will lead to more water removal compared to sodium removal.
The result will be hypernatremia, a powerful drive for thirst.
**Icodextrin – Mechanism of Action**

*Colloid osmosis* - analogous to the Starling force of albumin causing fluid flux from the interstitial to vascular compartment

\[
\Delta \pi = \Delta P
\]

Plasma osm = Interstitial osm
Dextrose vs Icodextrin

Crystalloid osmosis with dextrose

Blood side  Dialysate side

H2O movement

lower osmolality  higher osmolality

(aquaporin)
Dextrose vs Icodextrin

Colloid osmosis with icodextrin

H2O and solute movement

Blood side

Dialysate side

equal osmolality

no significant aquaporin activation with icodextrin
No Sodium Sieving with Icodextrin: Not all Ultrafiltrate is the Same

1 Liter of UF with dextrose

$[\text{Na}^+] \, 70$

1 Liter of UF with icodextrin

$[\text{Na}^+] \, 130$
Marvin on APD (Part I)

- Marvin is a 35 year old man with chronic GN who starts on APD, 2.0L X 3 exchanges over 8 hours at night, last fill 2L.
- Residual renal function is GFR 9 ml/min, $U_{\text{out}}$ 960 ml/24h.
- Typical UF on the cycler is 800 ml, average initial drain volume of his day dwell is 1700 ml when he goes on the cycler at night.
Which ONE Statement is FALSE?

a) He is protected from ECF volume overload in part by the residual urine volume.
b) He probably has borderline adequacy and should have his dialysis prescription increased, or be converted to hemodialysis.
c) He should be advised to avoid nephrotoxic insults, such as NSAID’s and COX-2 inhibitors.
d) Eight hours of APD is appropriate for many patients.
Which ONE Statement is FALSE?

a) He is protected from ECF volume overload in part by the residual urine volume.

b) He probably has borderline adequacy and should have his dialysis prescription increased, or be converted to hemodialysis.

c) He should be advised to avoid nephrotoxic insults, such as NSAID’s and COX-2 inhibitors.

d) Eight hours of APD is appropriate for many patients.
• Marvin is on a reasonable PD regimen (8.0 L/day)
• in addition, he has a lot of residual kidney function
• there should be no question of adequacy issues at this point
• (he would probably even thrive with a lower dose of PD)
Adequacy of Peritoneal Dialysis

The strength of PD lies in

– continuous therapy 24/7
– preservation of residual kidney function (RKF) compared to HD
– good middle molecule clearance (by RKF and the peritoneal membrane)

None of these is captured by Kt/V urea
Adequacy of Dialysis in PD

- randomized, controlled trials have not shown a survival benefit for any \( \text{Kt/V urea} > 1.5 \)
- lower limit for \( \text{Kt/V urea} \) unknown

Paniagua J Am Soc Neph 2002
Adequacy of Dialysis in PD

The KDOQI Guidelines in a Nutshell

- minimum total (renal + peritoneal) Kt/V urea of 1.7
- monitor and protect RKF
- careful attention to volume status
- trial of increased dialysis is indicated if patient not doing well without another explanation
Adequacy of Dialysis in PD

International Society for Peritoneal Dialysis practice recommendations: Prescribing high-quality goal-directed peritoneal dialysis
Fluid Balance in Peritoneal Dialysis

Intake

Na+ and water

Output

Urine and UF

Intake = Output

Ultrafiltration
Volume Overload in PD

• **Intake**
  – excessive salt and water consumption

• **Output**
  – loss of residual renal function
  – use of the wrong dialysis fluid
  – failure of peritoneal membrane to respond (true ultrafiltration failure)
  – mechanical problems like leaks
Volume Overload in PD

- **Output: Loss of Residual Kidney Function**
  - probably the commonest cause of progressive fluid overload
  - rate of loss of RRF is variable and unpredictable from patient to patient
  - use diuretics to augment urine Na\(^+\) & water output
    - eg furosemide, metolazone
Try to Protect the Kidney Function

– avoid NSAID’s, COX 2-inhibitors, dye studies, aminoglycosides, volume depletion
– continue immunosuppression for failed transplant kidneys that still have function

*Treat your dialysis patient with RKF just like you would your CKD 3 or 4 patient*
Volume Overload (continued)

- *Use of the wrong type of PD fluid*
  - usually this means failure to account for the risk of fluid absorption during the long dwell
Volume Overload (continued)

Tackling the long dwell:

1. Use icodextrin or a more hypertonic dialysate (e.g. 2.5%)
2. Break up the long dwell
   • Day dry (only if there is a lot of RRF)
   • “Mid-day” exchange in APD
   • Drain out day exchange in APD after a few hours
Fluid Absorption During the Long Dwell

Or, it may not need any intervention

• if there is a lot of urine volume, may compensate for fluid absorption
  – e.g. patient on APD
    • last fill 2L
    • initial drain 1.5 L (so .5L fluid absorption)
    • urine output 1.0 L
    • patient is clinically euvolemic

No Need to Change the Prescription
Volume Overload in PD

• Output dependent
  – failure of the peritoneal membrane to allow ultrafiltration (membrane failure)
  – mechanical failure of dialysis procedure (leaks, etc)
True Peritoneal Membrane Failure

- **Definition:** Inability to maintain volume homeostasis despite the use of hypertonic dialysate solutions (3 or more daily)
  
  or

- **Failure to ultrafilter > 400 ml using a 4.25% bag for 4 hours (the Rule of 4’s)**
True Peritoneal Membrane Failure

- on PET test, D/P creatinine is high
- these high transporters have rapid absorption of glucose across peritoneal membrane
- rapid dissipation of osmotic gradient
- poor ultrafiltration
Management of Rapid Transporters (I)

- reinforce salt and water restriction
- use more hypertonic dialysate
- icodextrin can be quite helpful here (as effective in high transporters as other transport types)
Management of Rapid Transporters (II)

- “push” residual urine output (diuretics)
- APD with dry day, or drain out last fill at lunch (if enough RRF)
- once anuric, watch closely for volume overload
- **consider transfer to hemodialysis if patient is chronically overloaded** (start talking about vascular access placement with the patient)
Volume Overload (continued)

- Output dependent
  - mechanical failure of dialysis procedure
Part II – Marvin Gets Puffy

• 1 year later, Marvin comes to clinic complaining of increasing ankle edema. The BP, which had been normal, is now 150/100.

• The dialysis prescription is unchanged. Serum creatinine, which had been 10.6 mg/dl at the start of dialysis, is now 13.8 mg/dl.
Which ONE Statement fits Marvin BEST?

a) The increased serum creatinine reflects a failure of solute transport across the peritoneum.

b) He most likely has peritonitis and the acquisition of a high transporter state.

c) The new onset hypertension is likely the result of acquired renal cystic disease.

d) Both the increased serum creatinine and peripheral edema can be explained by decreased residual kidney function.
Which One Statement fits Marvin BEST?

a) The increased serum creatinine reflects a failure of solute transport across the peritoneum.

b) He most likely has peritonitis and the acquisition of a high transporter state.

c) The new onset hypertension is likely the result of acquired renal cystic disease.

d) Both the increased serum creatinine and peripheral edema can be explained by decreased residual renal function.
Explanation

• A decrease in RKF (both solute clearance and salt and water excretion) would explain the changes in Marvin over the past year.

• An increase in serum creatinine is much more likely to be the result of a decrease in renal creatinine clearance than to membrane changes.
  – Peritoneal membranes tend to become more, not less, permeable to solutes over time.
Part II – Marvin Gets Puffy

How to help Marvin (APD 2.5L x3, 2L last fill)

- dietary salt restriction
- push diuretics
- last fill:
  - mid-day exchange, or
  - icodextrin last fill, or
  - both (ico X 10h, 2.5% X 6h)
Peritoneal Equilibration Test

- The “rapid transporter” has increased peritoneal vascularity and transports small solutes quickly; but loses glucose osmotic gradient quickly and may have problems with ultrafiltration
- “slow transporter” has slower removal of small solutes but better ultrafiltration
Summary of Important Points (II)

• short hypertonic PD dwells lead to removal of more water than sodium leading to hypernatremia
  – avoid short dwells except in rapid transporters

• residual kidney function is a more important predictor of outcome than dose of PD measured by small solute kinetics
  – try to protect residual function
  – don’t obsess about Kt/V – get at least to minimum target and obsess about RKF,volume status and quality of life
References

1. Paniagua R, Amato D, Vonesh E et al
   Effect of increasing peritoneal clearance on mortality rates in peritoneal dialysis: ADEMEX, a prospective randomized controlled trial

2. Perl J, Dember LM, Bargman JM et al
   The Use of a Multidimensional Measure of Dialysis Adequacy – Moving Beyond Small Solute Kinetics

3. Rodriguez-Carmona A and Perez Fontan M
   Sodium removal in patients undergoing CAPD
   *Perit Dial Int* 22: 705-13, 2002

4. Bargman JM
   Mistakes in Dialysis: We Use Kt/V As a Measure of Adequacy of Dialysis
   *Semin Dial* 29(4): 258-9, 2016

5. ISPD Guidelines: Prescribing High Quality Goal-Directed Peritoneal Dialysis
   *Perit Dial Int* 40 (3): 244-253, 2020