Anatomy and Physiology of Peritoneal Dialysis

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Outline

- Peritoneal cavity as a dialysis system

- Models of peritoneal transport

- Physiology of peritoneal transport
  - ➢ Inverse relationship between solute transport and ultrafiltration

- Kinetics of peritoneal transport

- Synthesis & Application

- Middle Molecules

Anatomy of The Peritoneum

- The lining of the abdominal cavity
- Two layers:

   parietal - lines the anterior wall and undersurface of
   the diaphragm
   - 20% of total SA; blood supply from
   abdominal wall

   visceral - covers the abdominal organs
   - 80% of total SA; blood supply from
   mesenteric aa and portal vv

Gokal R, Textbook of PD, pp. 61-70
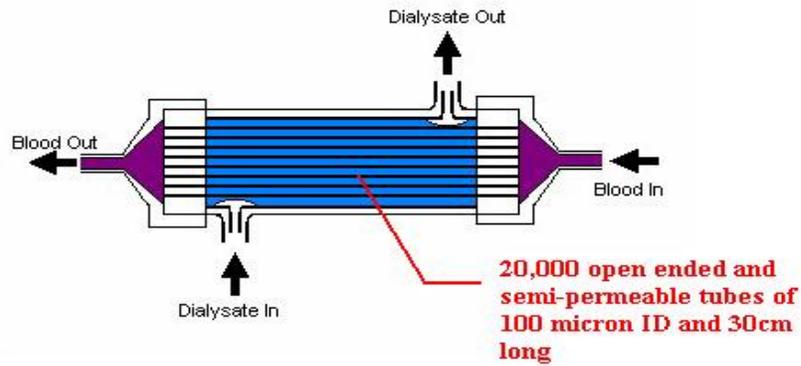
Anatomy of The Peritoneum

- Size 1.5 – 2 m^2; approximates BSA

- Highly Vascular

- Semi-permeable/bi-directional

- "Lymphatic" drainage through diaphragmatic stomata

- Continuous with Fallopian Tubes in females

Gokal R, Textbook of PD, pp. 61-70

1. The two main properties of the peritoneal membrane are:

   a. Semi permeable – this allows substances of certain sizes to move from an area of greater concentration to less   concentration.
   b. Bi Directional - substances move in either direction across the membrane.

2. So-called "lymphatic" drainage refers to bulk flow from the peritoneal cavity back to the circulation. This actually occurs across tissues as well as lymphatics. As this is convective flow, dissolved solutes move with the fluid. Thus, fluid reabsorption results in loss of solute clearance as well as loss of fluid removal.

3. It is important to be aware of the continuity of the peritoneal cavity with the Fallopian tubes as retrograde menstruation- which may occur in any woman but goes undetected- will cause bloody dialysate and create concern in the PD patient.

SCHEMATIC OF A HEMO-DIALYSIS DEVICE

Dialysate Out

Blood Out

Blood In

20,000 open ended and semi-permeable tubes of 100 micron ID and 30cm long

Dialysate In

source http://www.shodor.org/master/biomed/physio/dialysis/hemodialysis/fig2.jpg

In HD, blood is removed from the body and passed through a large number of small "capillary" tubes. The tubes are bathed by dialysate. Solutes diffuse from blood in the capillary tubes into dialysate and are discarded. Application of a transmembrane pressure gradient results in ultrafiltration of fluid from the capillary tubes into the dialysate and that fluid too is then discarded.

# The Peritoneal Cavity as a Dialysis System
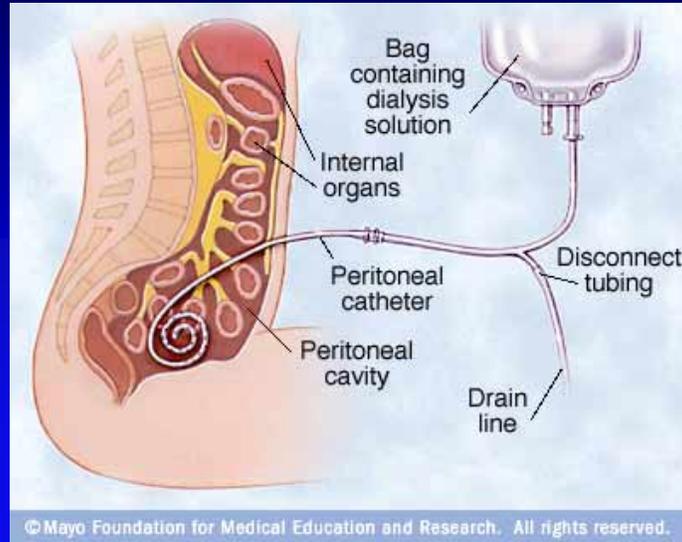
The same processes are utilized in peritoneal dialysis except that dialysate is introduced into the peritoneal cavity where it comes into contact with capillaries perfusing the peritoneum and viscera. Solutes diffuse from blood in the capillaries into the dialysate and are discarded. A transmembrane pressure gradient is applied- osmotically- and results in ultrafiltration of fluid from the capillary tubes into the dialysate; that fluid too is then discarded.

Transport Processes in Peritoneal Dialysis

Diffusion-

Movement of solute from an area of <u>higher</u> concentration to an area of <u>lower</u> concentration
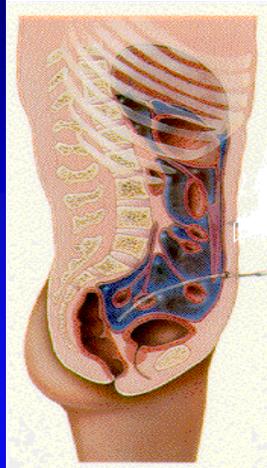
Osmosis-

Movement of water from an area of <u>higher</u> concentration (lower solute concentration) to an area of <u>lower</u> concentration (higher solute concentration)

Diffusion is created by having a concentration gradient on either side of a semipermeable membrane.

Solutes move from an area of greater concentration to less concentration.

Models of Peritoneal Transport

- The three pore model

- The pore- matrix model

- The distributed model

These models are not mutually exclusive; rather they should be viewed as complementary to one another.

Transport Across the Peritoneal Endothelium:
The Three Pore Model

- **Large pores (100 - 200 Å)**
  - few in number (3% of SA)
  - transport macromolecules
  - clefts between endothelial cells

- **Small pores (40 - 60 Å)**
  - most numerous (95% of SA)
  - allow transport of small solutes and water
  - postulated to be clefts in the endothelium; have not been demonstrated anatomically

Based upon the observed nature of solute and water transport across the peritoneum Rippe predicted the existence of 3 pores of different sizes: a large pore of 100- 200 Å corresponding to interendothelial cell clefts which allows for transport of even large molecular weight solutes; a small pore of 40-60 Å- that has yet to be demonstrated anatomically- which allows for transport of water and low molecular weight solutes and, as seen on the next slide…

Transport Across the Peritoneal Endothelium:
The Three Pore Model (cont'd)

- **Ultrasmall (transcellular) pores (4 - 6 Å)**
  - many in number (but only 2% of SA)
  - transport water only (Na sieving)
  - **Demonstrated** to be AQP 1

…an ultrasmall pore of 4-6 Å that allows for the passage of water only and NO solute. This pore has since been shown to be aquaporin 1 (AQP 1).

Water Transport in Aquaporin- 1 Knockout Mice
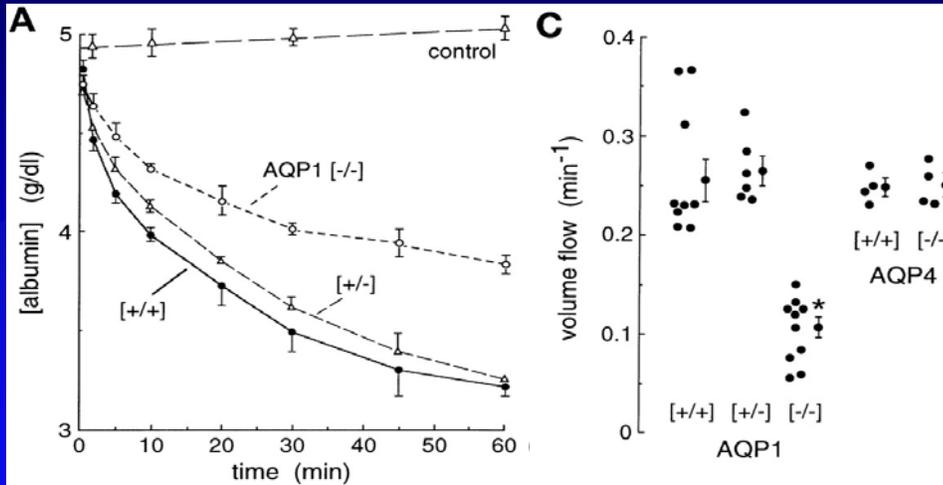
Yang et al. AJP 276:C76, 1999

When radiolabeled albumin is placed into the peritoneal cavity of a mouse in the absence of an osmotic gradient across the peritoneal membrane, the concentration of the albumin remains stable over the course of the next hour (control). When an osmotic gradient is imposed across the peritoneal membrane ultrafiltration of fluid from blood into the peritoneal cavity results in progressive dilution of the radiolabeled albumin; this is true whether the mouse is homozygous (+/+) or heterozygous (+/-) for AQP 1. However, if the mouse is totally devoid of AQP 1 (-/-) ultrafiltration is decreased by approximately 40% and the decrease in albumin concentration is therefore attenuated. As seen in the right panel of this slide, elimination of AQP 4 has no effect on ultrafiltration.

Changes In Dialysate Sodium During Dwell (Sodium Sieving)
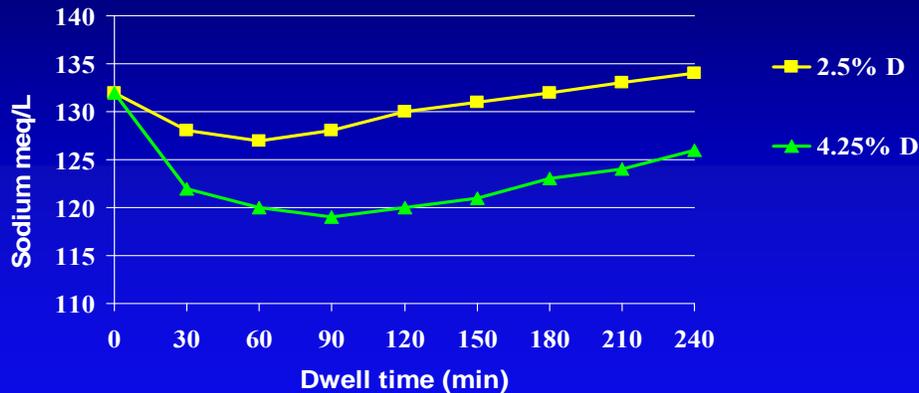
Heimburger et al. Kid Int 38: 495, 1990

Filtration of water alone in response to an osmotic gradient results in the process of sodium sieving. Early in a dwell, when the osmotic gradient is greatest, water moves into the peritoneal cavity via AQP 1 before any significant solute transport has taken place via the small or large pores. Excess water in the peritoneal cavity results in a decrease in the dialysate sodium. As the dwell progresses and sodium diffuses into the peritoneal cavity via the small and large pores the dialysate sodium increases once again. However, were the peritoneum to be drained early on while the dialysate sodium is low- and the process repeated several times- the loss of free water would ultimately culminate in hypernatremia.

Ultrafiltration in PD:
The Pore-Matrix Model
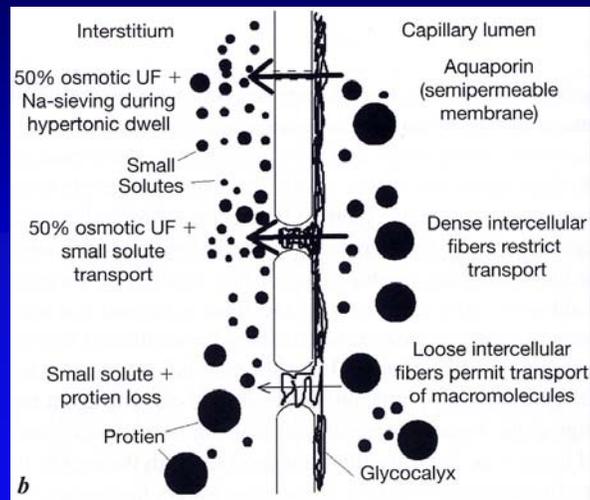
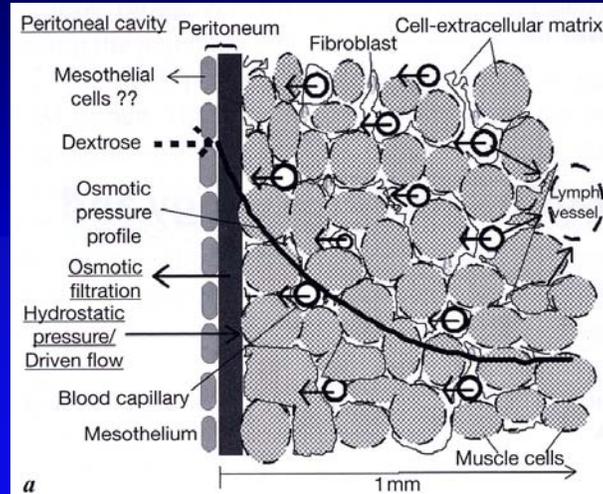
Flessner M. Contrib Nephrol 163:7, 2009

As indicated previously, the small pore has yet to be demonstrated anatomically. Borrowing from the study of other vascular endothelia Flessner has postulated that the large and small pores represent a single entity with the difference in transport characteristics being a function of the density of the intercellular glycoprotein matrix.

Ultrafiltration in PD:
The Pore-Matrix Model

- The small and large pores represent different functional states of a single entity that depends on the density of the glycocalyx.

- The glycocalyx density is decreased by:
  - Oxidized LDL
  - Adenosine
  - Ischemia reperfusion injury
  - TNF α

Ultrafiltration in PD: The Distributed Model

Flessner M. Contrib Nephrol 163:7, 2009

The distributed model postulates that the influence of a specific capillary on PD transport is a function of that capillary's proximity to the mesothelial/dialysate interface. Proliferation of vessels near the interface will increase "effective" peritoneal surface area.

Effective Peritoneal Surface Area

- Increased "effective" peritoneal surface area may occur:

    - During peritonitis

    - After prolonged exposure to high glucose-containing fluids
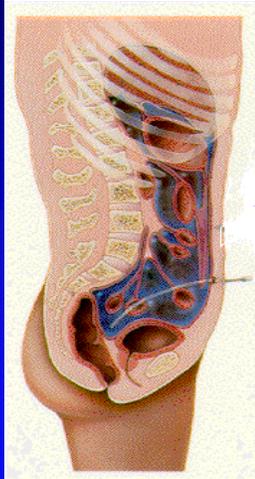
Two Clinical Endpoints for Peritoneal Transport

- **Solute Clearance**
  - ➤ diffusive
  - ➤ convective
- **Fluid Removal**

With this background, let us now begin to examine the clinical properties of peritoneal transport.

Factors Influencing Solute Diffusion

- Surface Area
- Peritoneal Permeability
- Solute Characteristics
- Concentration Gradient
- Temperature of Dialysis Solution
- Blood Flow
- Dialysis Solution Volume in 24 hrs.
- Dwell Time

There are eight key factors in diffusion occurring in Peritoneal Dialysis.

We will discuss them in detail in the next two slides.

The last two:
Dialysis solution volume in 24 hours and utilizing the full 24 hours for dwell time are the two ways to improve the efficiency of peritoneal dialysis.

Diffusion Curves for Solutes of Varying Size

Dialysate to plasma (D/P) ratios

Urea

Creatinine

MM

D/P_x

Dwell time (hours)
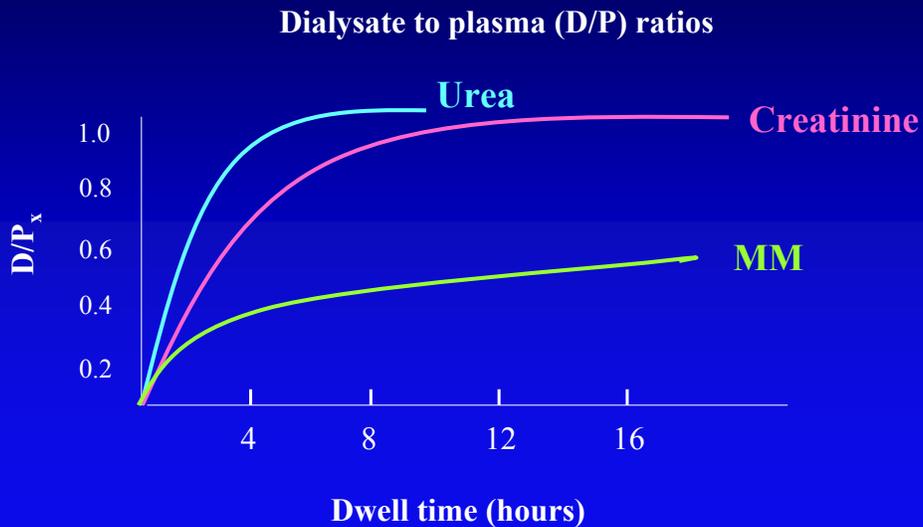
Note that urea, a very low molecular weight solute (60 Da) equilibrates very rapidly such that by 4 hours equilibration is virtually complete. Creatinine which is slightly larger (113 Da) lags somewhat behind urea but it too achieves nearly complete equilibrium within 4-6 hours. In contrast, note that middle molecular solutes (500- 5000) equilibrate much more slowly and their dialysate to plasma ratio (D/P) continues to increase even during a very long dwell.

Diffusion Kinetics –
From Blood to Dialysate

- Diffusive flux is highest in the first hour- the gradient is largest- and decreases over time

- By 4 hours, urea is > 90% equilibrated, creatinine > 60% equilibrated

- Further small solute removal is modest

- Long dwells more important for removal of *middle* MW solutes (e.g. β_2MG)

Factors Influencing Ultrafiltration

- Surface area

- Peritoneal membrane permeability

- Pressure gradients
    - hydrostatic
    - oncotic
    - osmotic (really hydrostatic; 1 mOsm = 17 mm Hg)

Water removal will also be affected by:
- Surface Area available
- The permeability of the membrane - Low Transport membranes
   remove more water because the dextrose remains longer in the PD solution.
- The glucose also creates a colloidal osmotic gradient between the blood
  and the PD solution removing water from the blood.

What Determines Transcapillary Ultrafiltration?

$$J_v = L_p\,S\,[P_{plasma} - P_{if} - \sum_{i,j}\alpha_j\sigma_{i,j}\,(\pi_{i,plasma} - \pi_{i,if})]$$

J_v	flow/area	α_j	Fraction of the total pore area that is made up of the jth pore
L_p	hydraulic conductivity		
S	total pore area	$\sigma_{i,j}$	Reflection coefficient of the jth pore for the ith solute
P_{plasma}	intraluminal capillary hydrostatic pressure in plasma	$\pi_{i,plasma}$	Osmotic pressure in plasma due to the ith solute
P_{if}	interstitial fluid hydrostatic pressure	$\pi_{i,if}$	Osmotic pressure in the interstitium due to the ith solute

Flessner M. Kid Int 69:1494, 2006

Transcapillary ultrafiltration (UF) is governed by Starling forces, accounting for each pore and each solute. Recall that σ (sigma), the reflection coefficient for a specific solute, refers to the fraction of molecules of solute "i" that, when they approach pore "j" will be bounced (or reflected) back and not allow to pass through. The higher the reflection coefficient, the more osmotically effective is that specific solute at that specific pore.

Or, in English…

Average UF rate (ml/min) =

hydraulic conductivity (cm/min/mmHg)   x
total effective pore area (cm^2)   x
[average osmotic pressure + net trans-membrane
hydrostatic pressure - net oncotic pressure (mm Hg)]

Factors Influencing Ultrafiltration

- Ideally we'd like to use a solute with reflection coefficient (RC) ~ 1.0. Glucose has a reflection coefficient of 1.0 for AQP-1 but this accounts for only 2% of SA.

- Despite having RC only ~ 0.05 for the small pore, adding glucose to PD fluid creates an osmotic gradient and moves water from the blood into the peritoneal cavity.

Water removal will also be affected by:
- Surface Area available
- The permeability of the membrane - Low Transport membranes
  remove more water because the dextrose remains longer in the PD solution.
- The glucose also creates a colloidal osmotic gradient between the blood
  and the PD solution removing water from the blood.

Effect of Glucose Absorption

Therefore, a major determinant of the average UF per exchange is the "average $\sigma_{glucose}$", as this will affect the rate of glucose absorption and the speed of decline of the glucose gradient.

Membrane Permeability and Ultrafiltration –
"slow transporters"

the *"tighter"* the peritoneal membrane (higher mean σ_{glu})

⬇

the *slower* will glucose diffuse out of the peritoneal cavity

⬇

the osmotic gradient will be maintained *longer*

⬇

the *more* ultrafiltration will take place

Membrane Permeability and Ultrafiltration – *"rapid transporters"*

the "*leakier*" the peritoneal membrane (lower mean σ_{glu})

the *faster* will glucose diffuse out of the peritoneal cavity

the *faster* the osmotic gradient will dissipate

the *less* ultrafiltration will take place

The Peritoneal Equilibration Test

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

- Quantified as $\dfrac{\text{Dialysate creatinine concentration}}{\text{Plasma creatinine concentration}}$

or

D/P creatinine (at t = 4 hours)

The nature of peritoneal transport in a given patient may be assessed by using the Peritoneal Equilibration Test, inititally developed by Dr. Zbylut Twardowski over 20 years ago. This test poses two questions.

1. How easily does solute (creatinine) cross from the blood to the peritoneal cavity?

The Peritoneal Equilibration Test

How long is glucose retained in the peritoneal cavity?

- Quantified as:

  Dialysate concentration of glucose at t = 4hrs

  Dialysate concentration of glucose at t = 0 hr

  or

  D/ D_0 glucose (at t = 4 hours)

- *cannot use D/P glucose as a surrogate since glucose entering the plasma from dialysate is rapidly metabolized*

2. How long is glucose retained in the peritoneal cavity?

Peritoneal Equilibration Test Protocol

- 2L of 2.5% dextrose dialysate is infused with the patient supine after complete drain of a long ($\geq$ 8 hrs) 2 L dwell.

- Blood and dialysate samples are taken immediately after infusion and at 2 and 4 hours for measurements of urea, creatinine, and glucose.

- Patient is drained upright after 4 hours and drain volume is recorded.

Standard Peritoneal Equilibration Test (2.5% Dextrose)
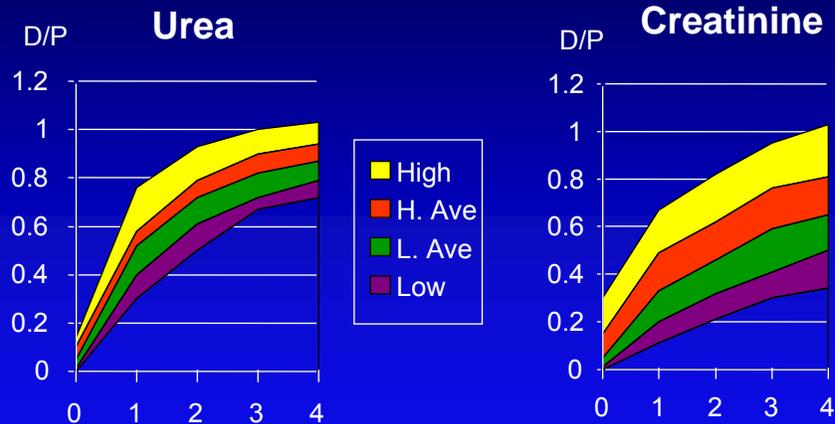
Twardowski et al. PDB 7; 138, 1987

Results are expressed in quartiles, from top to bottom:

➢>1 standard deviation (SD) above average

➢Within 1 SD above average

➢Within 1 SD below average

➢> 1 SD below average

Note that there is more discrimination achieved using creatinine than there is with urea as creatinine equilibrates somewhat more slowly.

Standard Peritoneal Equilibration Test (2.5% Dextrose)

Twardowski et al. PDB 7: 138, 1987

D/D_0 glucose is inversely related to D/P_{cr}. Those who most rapidly transport creatinine **into** the dialysate (yellow) most rapidly transport glucose **out** of the dialysate. Because they transport solute rapidly they will easily achieve adequate solute clearance; however, as they lose their osmotic gradient rapidly, they may have difficulty with ultrafiltration as a result. Conversely, those who transport creatinine into the dialysate **slowly** (purple) transport glucose out of the dialysate slowly as well. They maintain their osmotic gradient for an extended time and therefore do well with ultrafiltration; however, because of slow solute transport they may have more difficulty achieving adequate small solute clearance.
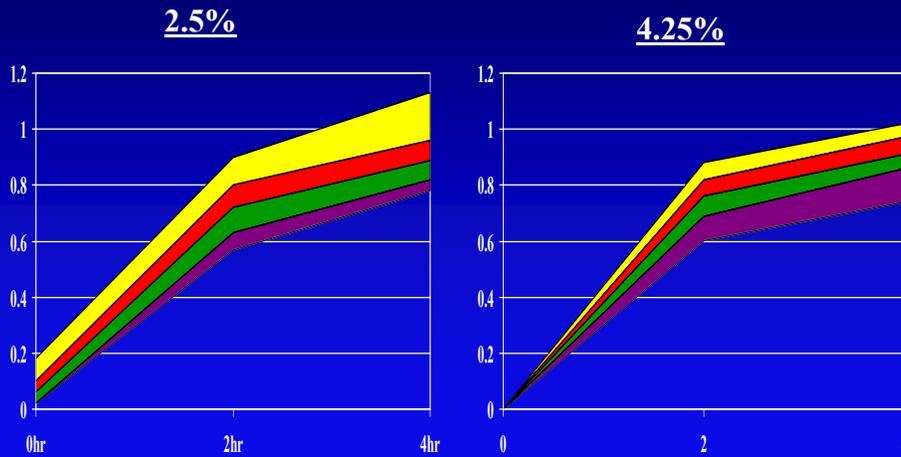
Modified Peritoneal Equilibration Test

- Similar to the standard PET except,

- Performed with 4.25% dextrose, thereby creating a large osmotic gradient.

Modified Peritoneal Equilibration Test

- Ultrafiltration failure is defined as net ultrafiltration < 400 cc at 4 hours
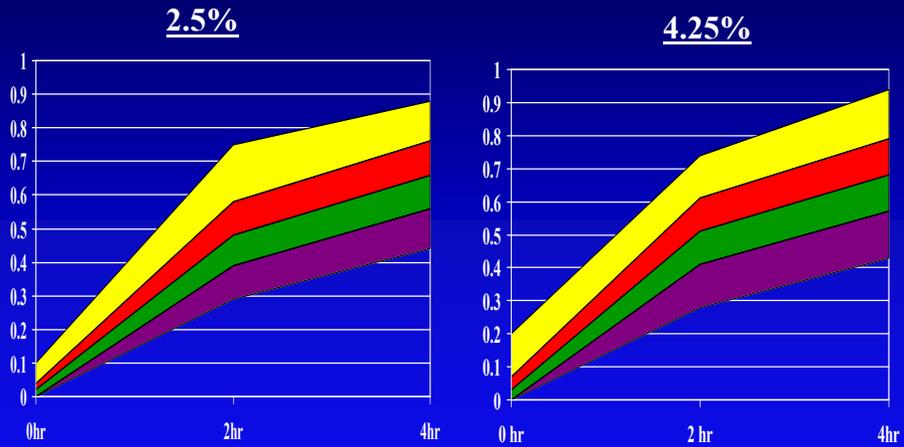
- Correlates well with clinical behavior.

Comparison of D/P Urea Obtained by 2.5% and 4.25% PET

Pride et al. Perit Dial Int 22:365, 2002

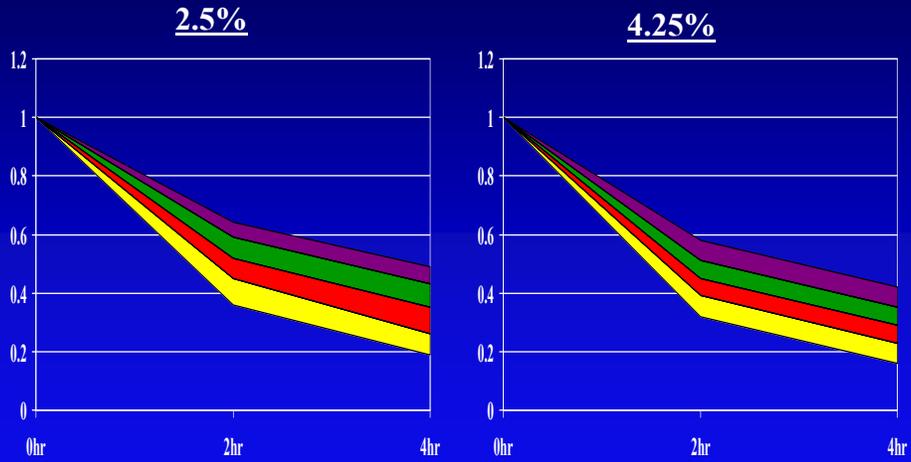Note that the general characteristics of the 2 sets of data are virtually identical for D/P_{urea}...

Comparison of D/P Creatinine Obtained by 2.5% and 4.25% PET

Pride et al. Perit Dial Int 22:365, 2002

…D/P$_{cr}$ …

Comparison of D/D$_0$ Glucose Obtained by 2.5% and 4.25% PET

Pride et al. Perit Dial Int 22:365, 2002

…and D/D$_0$glu.

Discordance (> 1 Category) Between 2.5% and 4.25% PET at 4 Hours

D/P_{urea}	3/47
D/P_{creat}	1/47
$D/D_{0\ glu}$	0/45

Pride et al. Perit Dial Int 22:365, 2002

In fact, the two data sets are nearly totally concordant. Therefore,

- A PET using 4.25% dextrose may be substituted for the standard 2.5% PET. This allows for simultaneous evaluation of both the small solute transfer and ultrafiltration capacities of the peritoneal membrane.

- However, commercially available programs for modeling peritoneal adequacy have not been standardized to the 4.25% PET.

When Should the PET be Performed?

- A PET performed during the first month of PD is often unreliable. This is especially likely if the initial PET shows the patient to be a low/average transporter.
- Therefore, the initial PET should ideally be done after 4-6 weeks of PD.
- A PET should not be done within a month of an episode of peritonitis.
- The PET need not be routinely repeated; it should be repeated only if clinically warranted.

Ultrafiltration with Different Strengths of Dialysate

4.25% Dextrose

1.5% Dextrose

Intraperitoneal volume, ml

Time, min
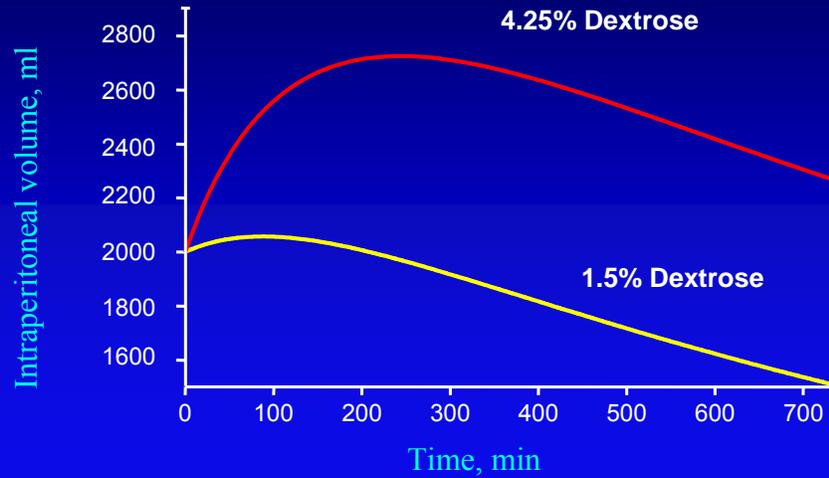
As expected, use of a larger osmotic gradient results in more rapid and greater UF during the initial phase of the dwell. Note however, that once peak intraperitoneal volume (IPV) is achieved the subsequent rate of decline in IPV is identical…
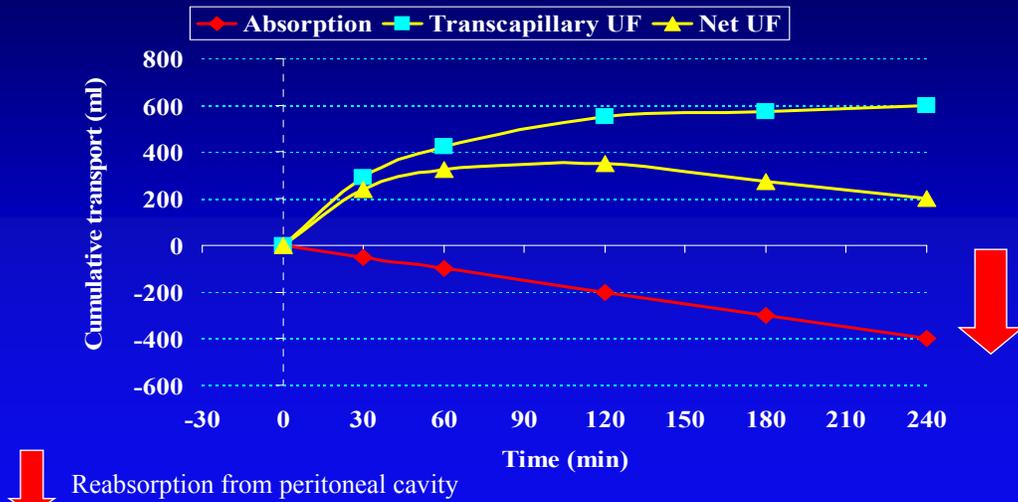
Fluid Absorption from the Peritoneal Cavity

- Occurs directly via lymphatics (~ 10%)

- Also via absorption across tissues

- Difficult to measure but ~ 1-2 ml/min

- These processes are "bulk flow" and therefore detract from solute and fluid removal

…due to fluid reabsorption from the peritoneal cavity. Though commonly referred to as "lymphatic reabsorption" this route in fact accounts for only a small percentage of total fluid absorption from the peritoneal cavity.

Balance of Opposing Forces

Legend: Absorption — Transcapillary UF — Net UF

Y-axis: Cumulative transport (ml), values 800, 600, 400, 200, 0, -200, -400, -600

X-axis: Time (min), values -30, 0, 30, 60, 90, 120, 150, 180, 210, 240

Reabsorption from peritoneal cavity

Mactier et al. JCI 80:1311, 1987

Thus, net UF (yellow triangles) is the algebraic sum of transcapillary UF (blue squares) + fluid reabsorption from the peritoneal cavity (red line- note that this is linear with time).

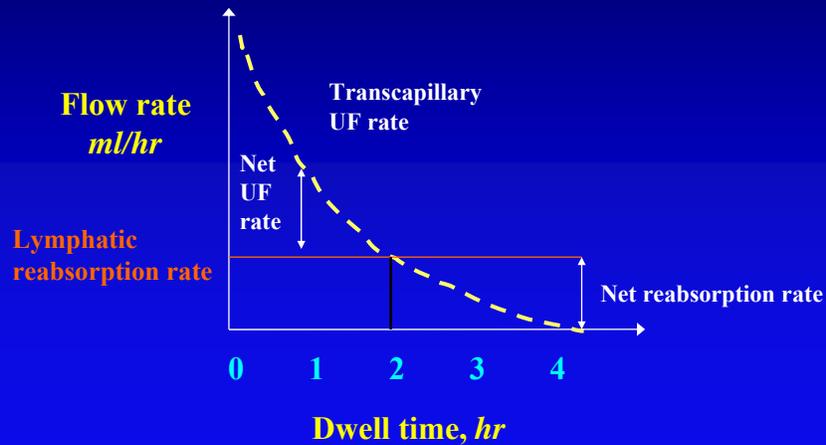## What Happens To Intraperitoneal (IP) Volume During a Dwell?

Assume 2L, average D/P, 2.5% Dextrose

- UF maximal at start (about 15 ml/min)
- UF decreases as glucose is absorbed from the peritoneal cavity and osmotic gradient lessens
- IP volume slowly increases until lymphatic reabsorption (LR) rate = UF rate
- Once LRR > UFR, IP volume begins to decrease
- After osmotic equilibrium is reached UF ceases; IP volume continues to decrease by virtue of LR

This slide describes the kinetics of a single dwell.

Net UF and Lymphatic Reabsorption Rates During 2.5% Dextrose Dialysis Dwell

Flow rate
ml/hr

Transcapillary
UF rate

Net
UF
rate

Lymphatic
reabsorption rate

Net reabsorption rate

0   1   2   3   4

Dwell time, *hr*

Mactier et al. Kid Int 32:165, 1987

This is demonstrated graphically on this slide. The ideal time to drain- peak IPV- occurs when transcapillary UF and LR rates are equal. Beyond this point in time IPV diminshes.

Net UF and Lymphatic Reabsorption Rates in a Low Transporter

Flow rate *ml/hr*

Transcapillary UF rate

Net UF rate

Lymphatic reabsorption rate

Net reabsorption rate

Dwell time, *hr*

0   1   2   3   4
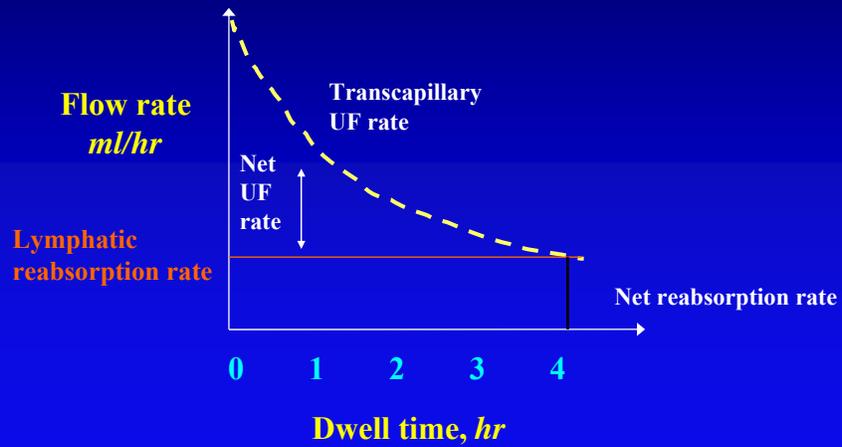
In a slow transporter, the time to peak IPV is prolonged and one may use longer dwells.

## Net UF and Lymphatic Reabsorption Rates in a High Transporter

Flow rate
ml/hr

Transcapillary
UF rate

Net
UF
rate

Lymphatic
reabsorption rate

Net reabsorption rate

0   1   2   3   4

Dwell time, *hr*
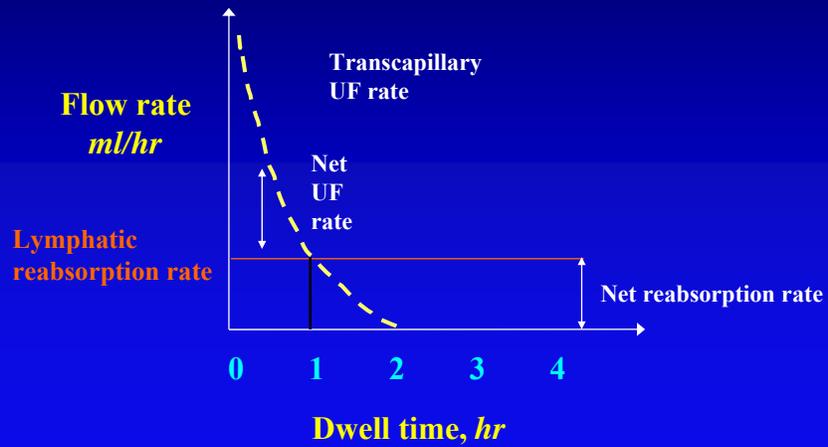
In contrast, in rapid transporters the time to peak IPV is short and net UF will be decreased because of LR if the dwell continues for too long.

Ultrafiltration Profile in a Patient with High Lymphatic Reabsorption Rate

Flow rate *ml/hr*

Transcapillary UF rate

Lymphatic reabsorption rate

Net reabsorption rate

Dwell time, *hr*
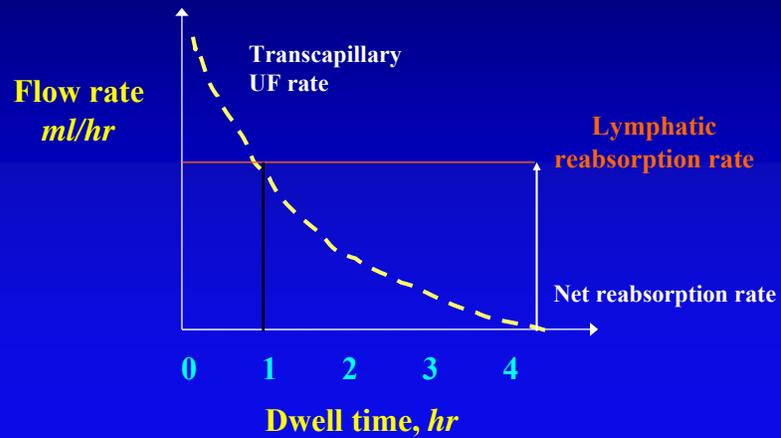
As seen here, high LR may also hasten the time to peak IPV and necessitate short dwells.

Net UF in a High Transporter with Increased Lymphatic Reabsorption

Flow rate *ml/hr*

Transcapillary UF rate

Lymphatic reabsorption rate

Net reabsorption rate

0   1   2   3   4

Dwell time, *hr*
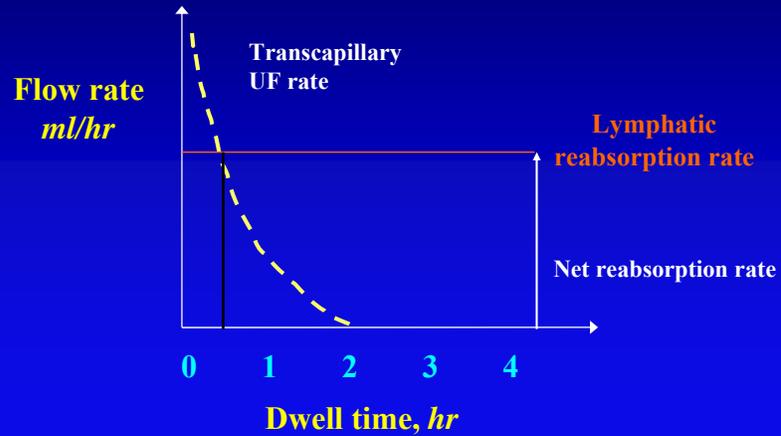
And someone who is both a rapid transporter and has high LR may have peak IPV occurring so rapidly that PD may not be suitable for ultrafiltration.

Temporal Profiles of CAPD and APD Prescriptions

CAPD

APD

Cycle 1 Cycle 2 Cycle 3 Cycle 4

nighttime period (9 hrs)   daytime period (15 hrs)
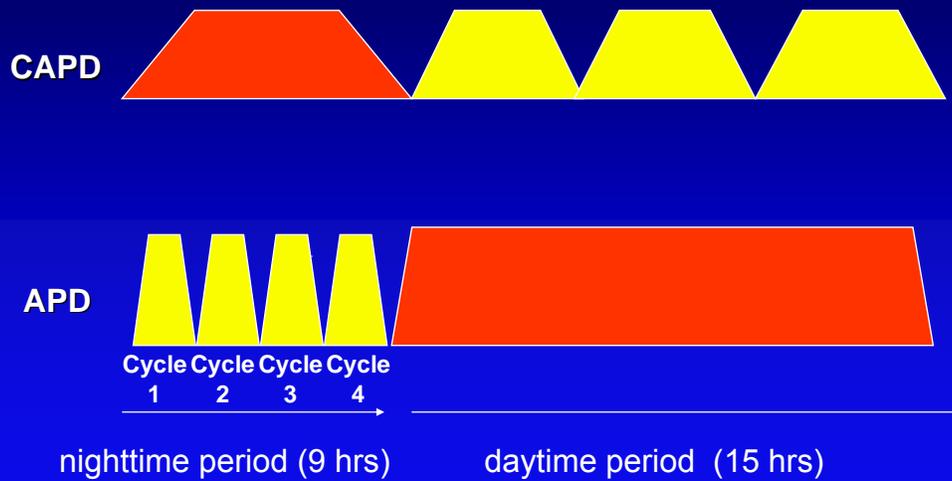
We must therefore tailor the prescription to the needs of each individual patient. By utilizing frequent short dwells overnight and only a single long daytime dwell it may be possible to achieve adequate ultrafiltration in a rapid transporter. Sometimes, however, the long daytime dwell- even if an exchange is added after 10 hours or so- proves excessively long and fluid reabsorption occurs. Under those circumstances the use of the alternative osmotic agent, icodextrin, may prove advantageous.

Features of the Alternative Osmotic Agent Icodextrin

- Glucose polymer with average MW around 16,000 Da.

- Effects ultrafiltration through the numerous small intercellular pores (reflection coefficient = 1.0).

Structure of Icodextrin

α (1→6) branch

Main α (1→4) chain
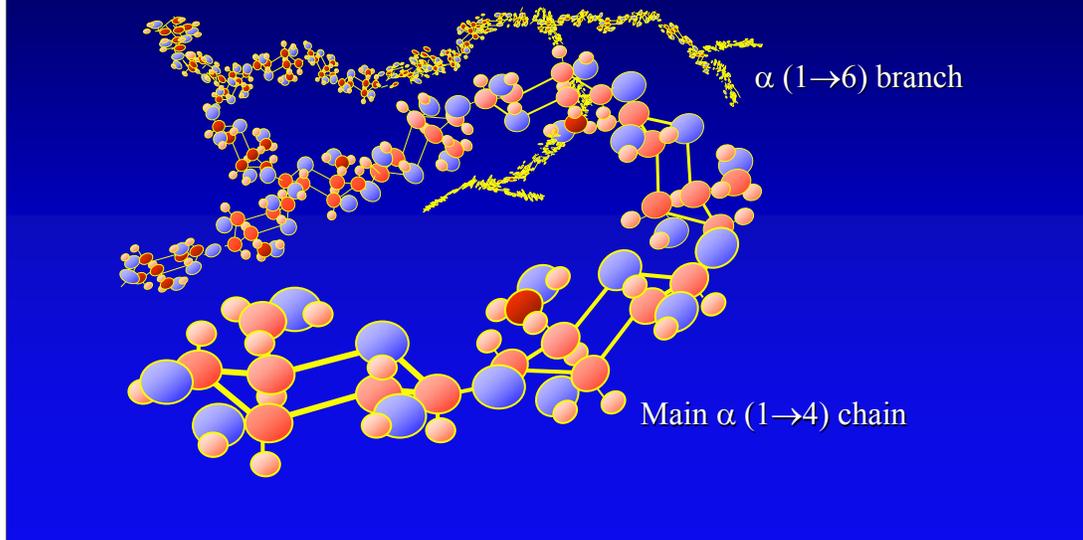
Icodextrin is a starch-derived high molecular weight (MW) glucose polymer that is structurally similar to glycogen. It consists of oligosaccharide polymers of D-glucopyranose linked by >90% α_{1-4} and <10% α_{1-6} glucosidic bonds.

Icodextrin differs from glycogen in that it has a lower percentage of $alpha_{1-6}$ linkages, and is thus not as highly branched. The average MW of icodextrin is approximately 16,000 Daltons.
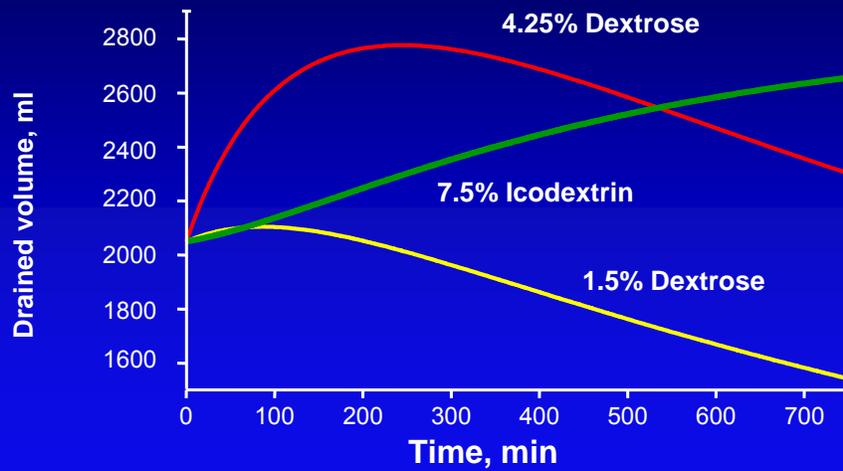
As a high molecular weight glucose polymer, icodextrin does not readily diffuse across the peritoneal membrane. Rather, it is slowly removed from the peritoneal cavity via lymphatic absorption. As a result, icodextrin is able to maintain osmotic forces and sustain ultrafiltration over longer dwell periods compared with conventional dextrose-based peritoneal dialysis solutions.

[1]Alsop MR. History, chemical, and pharmaceutical development of icodextrin. *Perit Dial Int.* 1994;14(suppl 2):S5-S12.

[2]Mistry CD, Gokal R. Optimal use of glucose polymer (icodextrin) in peritoneal dialysis. *Perit Dial Int.* 1996;16(suppl 2):S104-S108.

[3]Davies DS. Kinetics of icodextrin. *Perit Dial Int.* 1994;14(suppl 1):S45-S50.
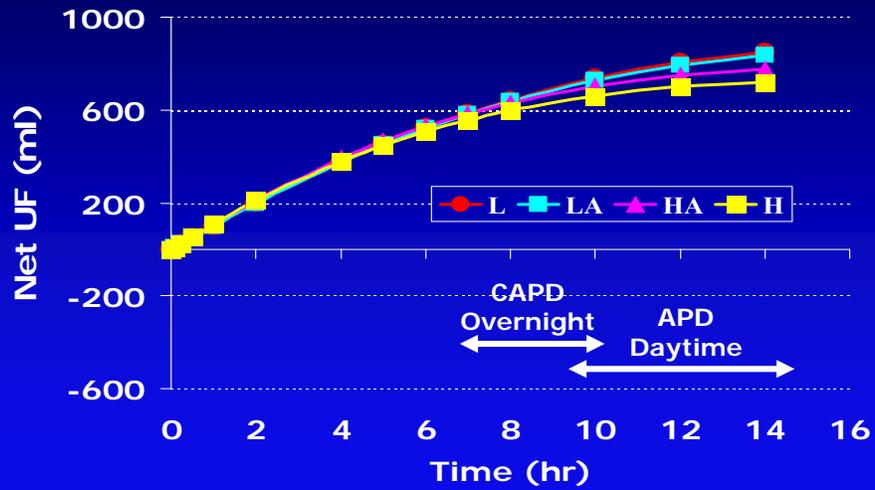
Temporal Profile of Ultrafiltration by Osmotic Agent

Drained volume, ml (y-axis): 1600, 1800, 2000, 2200, 2400, 2600, 2800

Time, min (x-axis): 0, 100, 200, 300, 400, 500, 600, 700

4.25% Dextrose

7.5% Icodextrin

1.5% Dextrose

Rippe and Levin. Kid Int 57: 2546, 2000

Note that icodextrin achieves IPV $\geq$ that achieved with 4.25% dextrose only if used for 8 hours or longer.

Because it is not absorbed across the peritoneal membrane the efffect of icodextin is the same regardless of transport status.

Composition of Icodextrin

	Standard	Icodextrin
Dextrose (g/dL)	1.5, 2.5, 4.25	---
Icodextrin (g/dL)	---	7.5
Sodium (mEq/L)	132.0	132.0
Chloride (mEq/L)	96.0	96.0
Calcium (mEq/L)	3.5	3.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	40.0	40.0
Osmolality (mOsm/kg)	346-485	282
pH	5.2	5.2

Note also that icodextrin achieves UF despite being isoosmolar with plasma.

Key Determinants of Average UF Rate

- Gradient of osmotic agent

- Average reflection coefficient of osmotic agent for small pores and for aquaporins

- Total pore area for small pores and aquaporins

Let us now review and synthesize what we have learned about ultrafiltration. The key determinants of UF are reviewed on this slide…

Reflection Coefficients

Large Pores (radius 250 Ang; 3% of pore area)
    Glucose 0
    Icodextrin 0

Small Pore (radius 40-50 Ang; 95% of pore area)
    Glucose 0.05
    Icodextrin 1.0

Aquaporins (3-5 Ang; 2% of pore area)
    Glucose 1.0
    Icodextrin 1.0

…and the reflection coefficients for glucose and icodextrin at the various pores are given on this slide.

Osmotic Gradients at Exchange Initiation

- 3.86% glucose = (38,600 mg/L) / 180 mg/mOsm = 214 mOsm/L in dialysate (d)
  - ➢ d-p = 214 - 5 = 209 mOsm/L gradient
- 7.5% icodextrin = 75000 mg/L / 16,000 mg/mOsm = 4.7 mOsm/L in dialysate (d)
  - ➢ d-p = 4.7 – 0 = 4.7 mOsm/L gradient

The initial osmotic gradients for 4.25% dextrose (which is 3.86% glucose; the remainder is water) and 7.5% icodextrin are calculated as shown.

Osmotic Pressure – Small Pores

Osmotic Pressure with glucose solution (mm Hg) =
$[0.05(gluc_d - gluc_p) + 0.05 (Na_d - Na_p) + 0.0 (urea_d - urea_p) + 0.05 (Cl_d - Cl_p) + etc] \times [17mm\ Hg/ mosm/L]$

*for icodextrin add $1.0(ico_d - ico_p)$ within first bracket

To calculate the osmotic pressure for a given solute across a given pore one must account for the osmolar gradient for that solute and its reflection coefficient at that pore. And then multiply by 17 to achieve the pressure.

Osmotic Pressure – Aquaporins

For both glucose and icodextrin solutions use the same equation as on the previous slide but use a reflection coefficient of 1.0 for each.

How Glucose Induces UF Across Aquaporins

- The reflection coefficient is 1.0

- The effective gradient is high (209 mOsm/L)

- The initial osmotic pressure is extremely high (209 x 17 = 3553 mm Hg).

- The above yields UF despite the very low pore area (2%).

Why Icodextrin Yields Only Minimal UF Via Aquaporins

- Although the reflection coefficient is high (1.0), the effective gradient is very low (4.7 mOsm/L).

- Initial osmotic pressure is low (4.7 x 17 = 80 mm Hg).

- Pore area is low (2%).

- Minimal UF rate does not decrease dialysate [Na] hence, no sieving.

Why Icodextrin Solutions Yield UF Even with Osmolality Less than that of Plasma

- The effective osmotic gradient due to icodextrin is more positive than the sums of any negative effective gradients for other solutes yielding a positive effective osmotic gradient.

- This results from the very low reflection coefficients for sodium, chloride, urea, etc.

- And this effect is exerted over a large pore area (97%).

## Possible Clinical Ramifications of Retained MMW Solutes in Uremia

Probably related to some long term complications of uremia:

- Dialysis acquired amyloidosis
- Accelerated CV risk profile
- Uremic platelet dysfunction
- Immunodeficiency

Let us close by briefly discussing the nature of middle molecule transport. Some of the possible clinical ramifications of middle molecular weight (WWM) solute transport are shown on this slide.

Diffusion Curves for Solutes of Varying Size

Dialysate to plasma (D/P) ratios
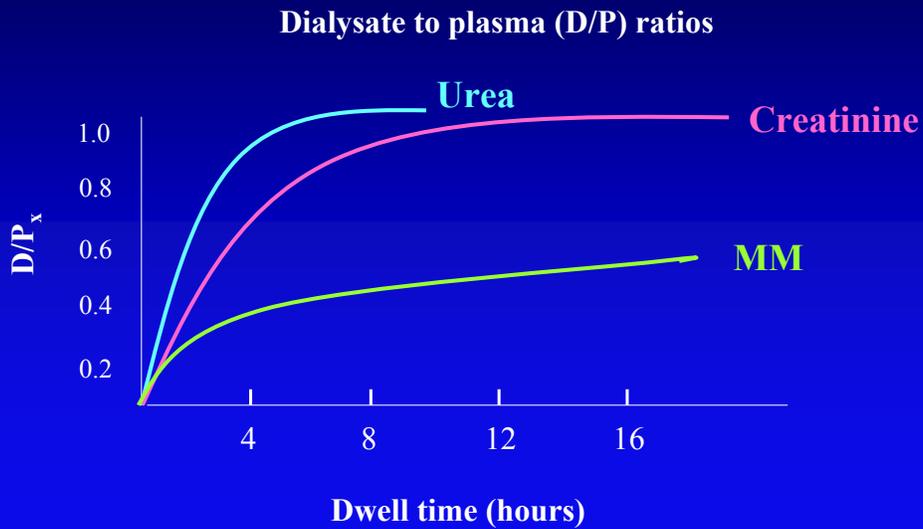
Recall that middle molecular solutes (500- 5000) equilibrate slowly and their dialysate to plasma ratio (D/P) continues to rise even during a very long dwell.

**Dissociation Between Clearances of Low and Middle Molecular Weight Solutes**
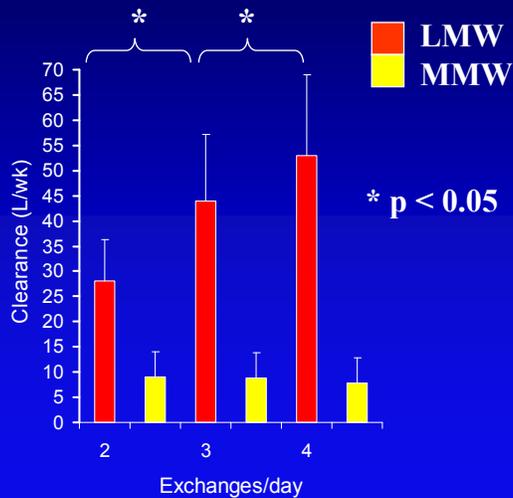
Kim et al. Perit Dial Int 21: 462, 2001

The importance of long dwell exchanges for the clearance of middle-sized molecules such as β_2-microglobulin was shown in a study that evaluated the impact of peritoneal dialysis (PD) schedule on middle molecule (β_2-microglobulin) and small molecule (creatinine) peritoneal clearance in 111 patients.

Results showed a significant linear increase in peritoneal clearance of creatinine with increasing number of daily exchanges. In contrast, as shown on this slide, clearance of β_2-microglobulin remained unchanged regardless of the number of exchanges.

[1]Kim DJ, Do JH, Huh W, Kim YG, Oh HY. Dissociation between clearances of small and middle molecules in incremental peritoneal dialysis. *Perit Dial Int*. 2001;21:462-466.

Middle Molecule Clearance is Dwell Time Dependent
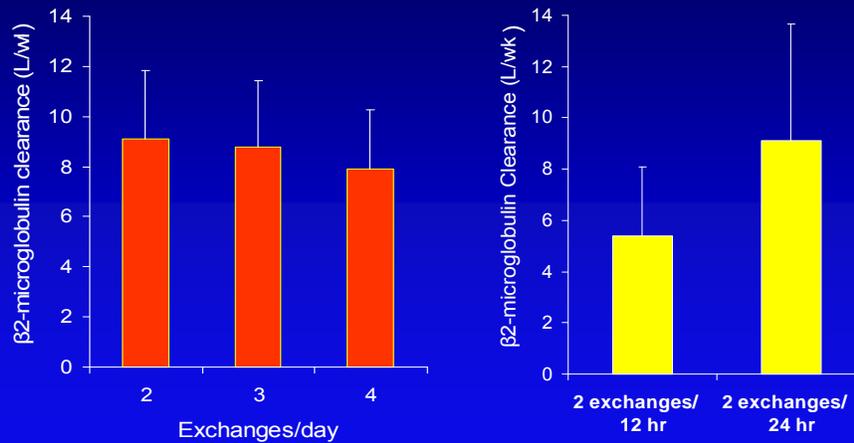
*p <.05 vs 2 exchanges/12 hr

Kim et al. Perit Dial Int 21: 462, 2001

However, in contrast to peritoneal clearance of creatinine, peritoneal clearance of β_2-microglobulin depended mainly on the total dwell hours of PD and not the number of exchanges. This slide shows that by changing the frequency of exchanges from 2 exchanges over 12 hours to 2 exchanges over 24 hours, clearance of β_2-microglobulin nearly doubled (from 5.4±2.7 L/wk with 2 exchanges over 12 hours to 9.5 ± 4.4 L/wk with the same 2 exchanges over 24 hours, P <.05).

[1]Kim DJ, Do JH, Huh W, Kim YG, Oh HY. Dissociation between clearances of small and middle molecules in incremental peritoneal dialysis. *Perit Dial Int*. 2001;21:462-466.

β₂-Microglobulin Clearance (4 hour dwell): Icodextrin *vs.* Dextrose
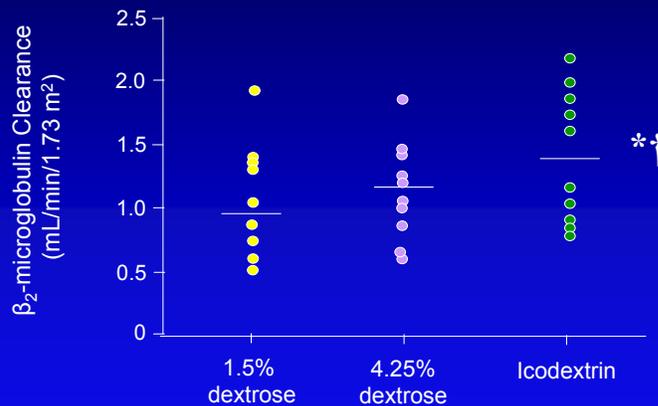
*p = 0.008, icodextrin *vs.* 1.5% dextrose
†p = 0.01, icodextrin *vs.* 4.25% dextrose

Ho- dac- Pannekeet et al. Kid Int 50: 979, 1996

A comparison of the effects of icodextrin, 1.5% dextrose, and 4.25% dextrose on fluid and solute kinetics was conducted in 10 stable CAPD patients. Standard permeability analyses (may be considered as similar to a PET test; 4-hour dwell) were performed with the three solutions within a period of 1 week.

The clearance of β_2-microglobulin was significantly higher with icodextrin (P =.008 vs 1.5% dextrose and P =.01 vs 4.25% dextrose. Use of icodextrin resulted in a 26% increase in β_2-microglobulin clearance compared to 4.25% dextrose, and a 44% increase compared to 1.5% dextrose.

The increased clearance of β_2-microglobulin with icodextrin is an indication that the glucose polymers exert their osmotic pressure mainly on the small pores resulting in increased convective clearance with icodextrin.

Ho-dac-Pannekeet MM, Schouten N, Langendijk MJ, et al. Peritoneal transport characteristics with glucose polymer based dialysate. *Kidney Int.* 1996;50:979-986.

Outline

- Peritoneal cavity as a dialysis system

- Models of peritoneal transport

- Physiology of peritoneal transport
  - Inverse relationship between solute transport and ultrafiltration

- Kinetics of peritoneal transport

- Synthesis & Application

- Middle Molecules

Question #1

- A patient is admitted in pulmonary edema and multiple rapid PD exchanges with 4.25% dextrose are performed. Which of the following may ensue as a consequence of sodium sieving?
    - A. Hyponatremia due to rapid water transport from dialysate to plasma via aquaporins.
    - B.Hypernatremia due to rapid sodium entry from dialysate to plasma via the small pores.
    - C. Hypernatremia due to rapid water transport from plasma to dialysate via aquaporins.
    - D. Hypokalemia due to rapid Na/ K exchange by Na/K ATPase in the mesothelium.

Question #1: Answer

- The correct answer is "C". When doing very hypertonic exchanges, e.g. with 4.25%, free water moves via the aquaporins from blood into dialysate, leaving behind Na in excess of water. If one performs multiple such exchanges in short order this may culminate in hypernatremia.

Question #2

- A patient has a 4 hour D/Pcr of 0.88 and D/D0 glucose of 0.35. Which of the following best describes the anticipated clinical findings using 1.5% dextrose dialysate and CAPD?

    - A. Good solute clearance and good ultrafiltration.
    - B. Poor solute clearance and good ultrafiltration.
    - C. Poor solute clearance and poor ultrafiltration.
    - D. Good solute clearance and poor ultrafiltration.

Question #2: Answer

- The correct answer is "D". The 4 hour D/Pcr of 0.88 and D/D0 glucose of 0.35 are indicative of a very rapid transporter. This individual would therefore be expected to have good solute clearance. However, s/he would dissipate the glucose- induced osmotic gradient very rapidly and would therefore be likely to absorb fluid from the abdominal cavity resulting in poor ultrafiltration