Peritoneal dialysis: principles, techniques, materials and quality control

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CONTENT

• General Principles of PD
• The Peritoneal Membrane: Anatomy
• Physiology of Peritoneal Dialysis: Diffusion, Convection, UF and PD prescription
• Take home messages

Schematic Principles of Peritoneal dialysis
Overview: how to start a PD patient

- Having a PD program
- Select patients for PD
  - Pre-ESRD education program
  - Pro/con evaluation of suitability of an individual patient
- Catheter placement
- How to start?
Objectives of a Pre-dialysis education Program

- Decrease mystique around dialysis
- Provide objective information
- Help make treatment choice
- Promote self care

Pre-dialysis education Program at St Luc

- Information provided by nurses in charge of self-care
- Individual
- In-house DVD
- Brochures
- Contact with experienced patients

Pre-dialysis education Program at St Luc

- All incident patients (n = 242) - 185 informed (57 not informed in-centre HD)
- First RRT modality
- Inclusion period: 12/94 - 3/00 (64 months)
- Exclusion criteria:
  ✔ Transfer
  ✔ Graft failure

Goovaerts T et al Nephrol Dial Transplant 2005
Our Pre-dialysis education program

- In-center HD: 40%
- PD: 31%
- sat. Unit: 16%
- Home HD: 9%
- TP: 4%

Goovaerts T et al Nephrol Dial Transplant 2005

Contra-indications to PD

- Stomias
- Enormous ADPKD kidneys
- Loss of integrity of the peritoneal membrane

The PD catheter

Courtesy of L Van Overmeire
The PD catheter
Right parietal access is preferable

PD catheter migration

The PD catheter
No evidence for superiority of one single type of catheter

Use of cuffed catheters to be preferred; no difference single vs double cuff

Use of Swann neck to be preferred

No preference for straight line or curled

Surgical or bed-site placement
Pre-sternal PD catheter in obese patients

Continuous Ambulatory Peritoneal Dialysis

Continuous Ambulatory Peritoneal Dialysis
Anatomy of the Peritoneal Membrane

The Peritoneal Membrane

- Mesothelium
- Interstitium - MPS hydrogel + collagen
- Capillary network - endothelial barrier

Peritoneal cavity - Reflections of the peritoneum

Virtual cavity (~100 ml of viscous fluid) between visceral and parietal sheets

C 1999 Wesley Norman
Nature of the Peritoneal Membrane

Serous membrane: reduces friction between moving organs
Components:
- Monolayer of mesothelial cells
- Connective tissue: matrix of collagen
  - Blood vessels - capillaries
  - Lymphatics
  - Cells: leukocytes, mastocytes
  - Nerve fibers
Thin membrane: 30-40 μm omentum (thicker in PP - VP)
1.0 - 1.3 square-meter
Contribution to transport: PP >> VP

Peritoneal membrane: the mesothelium

- Flat cells that form a monolayer: 2.5 - 3 μm thick (mesentery)
- Transitional mesothelium (parietal peritoneum): 10 - 15 μm thick
- Discontinuous basement membrane: type IV collagen
- Ultrastructure:
  - Intercellular junctions (tight-gap)
  - Basolateral invaginations
  - Microvilli and primary cilia
  - Rich in organelles

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Role of the Mesothelium

- Not a barrier for water and solutes transport
- Protection, host-defense mechanisms
- Regulation of inflammation, angiogenesis, healing - fibrosis
- Secretion of lipids: surfactant - phosphatidylcholine
- Secretion of cytokines, growth factors, PGs
- Secretion of collagen, fibronectin, elastin
- Marker: CA125

Mesothelial cell mass and CA 125

The submesothelial layer

- Matrix of collagen (bundles) and elastic fibers
- Many different cell types:
  - Mast cells, macrophages, leukocytes
  - Fibroblasts
  - Adipocytes
  - Blood vessels
  - Lymphatics
  - Nerve fibers
Vascularization of the Peritoneum

- **Visceral peritoneum:**
  - Upper mesenteric artery
  - Venous return via the portal system

- **Parietal peritoneum:**
  - Intercostal, epigastric and lumbar arteries
  - Venous return via vena cava system
  - Lymphatic network (fluid reabsorption)

The capillary network in the PM

Blood Flow to the Peritoneal Membrane

- Splanchnic blood flow rate: 25% of cardiac output
  - 1200 ml/min

- Peritoneal blood flow rate: 70-80 ml/min
Lymphatics in the peritoneal Membrane

Gokul et al. Textbook of PD 2000

Changes in the Peritoneal Membrane
Exposed to Peritoneal Dialysis

Structure of the Peritoneal Membrane

Factor VIII staining

Long-term PD

Submesothelial fibrosis  Vascular proliferation
Laparoscopy: 7 years of peritoneal dialysis

Loss of mesothelial cells after 40 days of PD

CA 125 and long-term (conventional) PD

\[ \text{Graphs showing CA 125 levels over time for different PD durations.} \]
The Peritoneal Membrane in the long-term PD

Submesothelial fibrosis

Vascular proliferation

Factor VIII staining

Combet et al. JASN 11, 2000

Biopsy Registry: submesothelial Fibrosis

Thickness submesothelial zone (mm)

Peritoneal Dialysis (months)

Williams JD et al. JASN 13:470-9, 2002

Correlation between Vascular Proliferation and Fibrosis in Long-term PD

Number of vessels/field

Matejtsen et al. PDI 19, 1999
**Simple peritoneal sclerosis**

- Modest sclerosis - restricted to submesothelial area
- No involvement of abdominal viscera and vessels
- Sometimes inflammatory infiltrate

**Sclerosing peritonitis**

- Sclerosis of the whole peritoneum
- Involves abdominal viscera and affecting large vessels
- Fibroblasts proliferation - collagen hyperplasia - inflammation

**VEGF distribution in the peritoneum**

- Combet S et al. JASN 11, 2000

Monoclonal anti-VEGF 165
Deposition of AGE’s (pentosidine staining)

Accumulation in mesothelium and endothelium

Changes in the Peritoneal Membrane during an Acute Peritonitis

Acute peritonitis: structural changes

Rat model - Catheter-induced peritonitis - 5 days

Inflammatory infiltrate

Vascular proliferation
Peritoneal Dialysis: principles and physiology

The Peritoneal Membrane
The Peritoneal Membrane

Source: Gambro

The peritoneal membrane consists of three main barriers to transport:
1. the capillary wall
2. the interstitium
3. the mesothelium

Ultrasmall pores: r < 3Å
Small pores: r 30-50 Å
Large pores: r > 150 Å

Mechanisms of Solute and Water Transport across the Peritoneal Membrane

1. Diffusion: passive movement along the concentration gradient
2. Solvent drag: convective transport of solutes with water
3. Net ultrafiltration: results of Starling forces:
   - transcapillary ultrafiltration
   - backfiltration into capillaries + uptake by lymphatics
**Diffusion across the Peritoneal Membrane**

- **Diffusion**: passive movement along the concentration gradient
- **Rate of solute transfer** \( (J_s) \) depends from:
  - Diffusive permeability of the PM to that solute \( (D_f/\Delta x) \)
  - Surface area \( (A) \)
  - Concentration gradient \( (\Delta C = P - D) \)

\[
J_s = \frac{D_f}{\Delta x} \times A \times \Delta C
\]

- **MTAC**: diffusive permeability x surface area

\[
J_s = \frac{D_f}{\Delta x} \times A \times \Delta C
\]

\[
MTAC = \frac{D_f}{\Delta x} \times A
\]

\[
J_s = MTAC \times (P - D)
\]

**Convective transport across the Peritoneal Membrane**

- **Convection**: Solvent drag, transport of solutes with water
- **Rate of solute transfer** \( (J_s) \) depends from:
  - Water flux \( (J_v) \)
  - Solute concentration in the membrane \( (C) \)
  - Solute reflection coefficient \( (\sigma) \)

\[
J_s = J_v \times C \times (1 - \sigma)
\]

\( \sigma \) varies between 0 : no resistance of the PM to transport
1 : ideal semi-permeable membrane

**Relationship between MW and MTAC**

- Diagram showing the relationship between logarithmic molecular weight and MTAC for various solutes (Urea, Creatinine, Urate, Inulin, beta 2-M)
Relationship between MW and MTAC

- Small solutes (urea, glucose, creatinine) diffuse freely across the PM
- Maximal transport determined by the surface area
- Notion of Effective Peritoneal Surface Area (EPSA)
  Number of perfused capillaries - pores
  Basal state only 25% capillaries perfused
  The MTAC of small solutes = functional measurement of EPSA

Transport of Macromolecules (e.g. Albumin)

- Much lower rate than LMW solutes and sodium
- Size-selective restriction
- Depends from surface area and size-selective pores
- Convection/restricted diffusion + large pores
- Increased during acute peritonitis: vasoactive mediators
Evaluation of the diffusive properties of the Peritoneal Membrane: the Peritoneal Equilibration Test

The Peritoneal Equilibration Test
Twardowski

The Peritoneal Equilibration Test

D/P creat

D/D0 Glucose
The Peritoneal Equilibration Test

Hyperpermeability - Fast transport status:
- good clearances
- poor UF

Use APD & icodextrin

Hyperpermeability - Low transport status:
- low clearances
- high UF
Inverse Correlation between Ultrafiltration and Blood Vessels (Chronic Infusion Rodent Models)

Margetts et al. JASN 13: 721-8, 2002

What would be your preferred type of Peritoneal Membrane?

The problem of the Fast Transporters

Churchill et al. CANUSA Study JASN 1998
The problem of the Fast Transporters

- Early glucose absorption; i.e. rapid dissipation of the osmotic gradient and, fluid retention.
- Important protein loss within the dialysate.
- Association with markers of inflammation, diabetes and co-morbid conditions.

Inherent Fast Transport Status

Patients with older age, diabetes, higher BMI and comorbid conditions are more likely to be fast transporters:
- Rumpsfeld et al; Am J Kid Dis 2004
- ANZDATA registry (n: 3185)
- Davies Kidney Int; 2004 (n: 574)
- Gillerot et al Kidney Int 2005 (n: 152)
- Clerbaux et al NDT 2006 (n: 72)

Comorbidity grade

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Serum albumin (g/dl)

![Graph](Gillerot et al Kidney Int 2005)

MTAC creat (ml/min/1.73m²)

Pearson r = -0.22
P = 0.005

Gillerot et al Kidney Int 2005

Polymorphism IL-6 G⁻¹⁷⁴C

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N = 152

Gillerot et al Kidney Int 2005
Ultrafiltration in Peritoneal Dialysis

Net UF = Cumulative TCUF – fluid uptake by lymphatics

Starling Forces and Fluid Transport

Transcapillary ultrafiltration rate = UFC (ΔP - Δπ + σ ΔO)

UFC: peritoneal UF coefficient
ΔP: hydrostatic pressure gradient
Δπ: colloid pressure gradient
σ: reflection coefficient: index of osmotic effectiveness (0 to 1)
ΔO: crystalloid osmolality gradient

σ Glucose = 0.02 – 0.05
(ultrasmall pores σ = 1 ↔ large pores σ = 0)
Water Transport across the Peritoneal Membrane

Small pores: radius 30–50 Å° (water + small solutes)
Paracellular pathway (interendothelial clefts)
50% UF: hydrostatic + colloid forces

Ultrasmall pores: radius < 3 Å° (selectivity for water)
Transcellular pathway: endothelial cell
50% UF: crystalloid osmosis
Predicted to mediate sodium sieving

Rippe et al. Kidney Int 40; 1991

The Sodium Sieving

Free-water movement: fall in dialysate sodium

Zweers et al; PDI 1999; 15: 65-72

Aquaporin-1 distribution in the PM

→ Structure: narrow pore 3.0 Å
→ Specificity for water only (no urea, glucose)
→ Distribution in endothelium

The role of Aquaporin-1 in the PM

Crystalloid vs Colloid Osmosis
or
Glucose-based dialysates vs Icodextrin

The Osmotic Gradient across the PM

Courtesy of Dr J Morelle

Ni et al; Kidney Int 2006
The Osmotic Gradient across the PM

Courtesy of Dr J Morelle

The Osmotic Gradient across the PM

Courtesy of Dr J Morelle
Physiopathological evolution of the Peritoneal Membrane with time on PD

Adapted from Lopez-Cabrea et al. (2006)

Solute Transport increases with Time on PD

Clerbaux et al Nephrol Dial Transplant 2006
Peritonitis induce functional and structural peritoneal membrane alterations

Davies et al. Nephrol Dial Transplant 1996
Williams et al. Kidney Int 2003

Peritoneal alterations with time on PD: Ultrafiltration failure

Increased vascularization - EPSA
Deficit - dysfunction in AQP1 (nb ? Quality ?)
Both together

Ultrafiltration failure: Aquaporin dysfunction

Murata et al. Nature 2000
The role of Aquaporin-1 in the PM

Goffin et al Am J Kidney Dis 1999

Loss of sodium sieving  AQP1 dysfunction (normal expression)

Peritoneal alterations with time on PD:  
Ultrafiltration failure

Increased vascularization - EPSA
Deficit - dysfunction in AQP1 (nb ? Quality?):
Both together
Increased lymphatic absorption
Changes in extracellular matrix: alteration of glucose conductance
How to monitor the Peritoneal Membrane Properties

Peritoneal Equilibration Test
Using 3.86 % glucose-based dialysate for UF volume and sodium sieving determinations
At PD onset
Yearly
After a « bad » peritonitis

How to monitor the Peritoneal Membrane Properties ? The mini-PET

How ?
Idem PET 3,86% with dialysate samplings at 0 et 60 min

Advantages
Calculation :
- Free Water Transport (FWT) within the total UF at 60 min
- Na removal
- D/P creat and D/D0 glucose
- Length : 60 min
How to monitor the Peritoneal Membrane Properties? The mini-PET

Free water transport (mL) = Total UF (mL) - UFSP (mL)

UFSP (mL) = $\frac{[NaR (\text{mmol}) \times 1000]}{\text{Ni}}$

where $NaR$ (mmol) was sodium removal, calculated as:

$[\text{Volume}_{\text{Input}} (L) \times \text{Na}\text{in}_{\text{Input}} (\text{mmol/L})]$

$- [\text{Volume}_{\text{Out}} (L) \times \text{Na}\text{in}_{\text{Output}} (\text{mmol/L})]$


How to monitor the Peritoneal Membrane Properties? The Osmotic conductance

Determine the power of glucose to generate an UF

2 successive Mini-PET:

1° glucose 1.36%
2° glucose 3.86%

Osmotic glucose conductance (OGC) in ml/min per mm Hg

$\text{OGC} = \frac{[V_{1\text{hr}} - V_{1\text{hr}}]}{[19.3 \times (G_{1\text{hr}} - G_{2\text{hr}}) \times t]} \times 1.7$

How to monitor the Dialysis efficacy

Ademex study
How to monitor the Dialysis efficacy

Ademex study

How to monitor the Dialysis efficacy

Ademex study

How to monitor the Dialysis efficacy

Lo WK et al Kidney Int 2003
How to monitor the Dialysis efficacy

- Control of anemia
- Control of BP
- Prevention of osteodystrophy
- Nutritional status

- PD adequacy
- Prevention of acid-base disorders
- Prevention of neuropathy
- Prevention of amyloidosis

- Quality of life
- Toxins epuration

Adapted from PY Durand

The PD prescription
The PD prescription

Residual renal function?
CAPD vs APD?
Number of dwells? Length of dwells? Tonicity of dwells?
Volume of dialysate?
Use of icodextrin from the start?

Residual renal function

- Provides endocrine functions
  - Erythropoietin production
  - Ca++, phosphorus and vitamin D homeostasis
- Contributes to total solute clearance (1 ml/min CrCl = 10 liter CrCl/week)
- Improves β2-microglobulin and middle molecule clearance
- Reduces mortality
- Improves QOL
- Allows for more liberal diet and fluid intake
- Increases nutritional status
- Facilities volume control

The Peritoneal Equilibration Test

- Hyperpermeability: Fast transport status:
  - good clearances
  - poor UF
- Use APD & icodextrin

Courtesy of B Bammens
The Peritoneal Equilibration Test

Hypopermeability—Low transporter status:
- low clearances
- high UF

The Intra Peritoneal Pressure

Relationship between IPP and IPV

Kaplan-Meier estimation of survival free of peritonitis when IPP day < or ≥ 13 cm H2O

Kaplan-Meier estimation of survival free of peritonitis when IPP night < or ≥ 14 cm H2O

Dejardin A et al Nephrol Dial Transplant 2007
The Intra Peritoneal Pressure

Avoid > 17 cm H$_2$O !!! (at rest)

<table>
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Use of icodextrin from the start ?

Fluid control: icodextrin vs glucose based dialysates

Preservation of the peritoneal membrane: the EAPOS study: icodextrin vs no icodextrin

By using APD, it is possible to achieve sufficient small solute clearance and UF to treat successfully even anuric patients.

Use of icodextrin from the start ?