Increasing sodium removal on peritoneal dialysis: applying dialysis mechanics to the peritoneal dialysis prescription

Michel Fischbach[1], Claus Peter Schmitt[2], Rukshana Shroff[3], Ariane Zaloszyc[1] and Bradley A. Warady[4]

[1]Service de Pédiatrie 1, Centre Hospitalier Universitaire Hautepierre, Strasbourg, France; [2]Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany; [3]Renal Unit, Great Ormond Street Hospital for Children National Health Service Foundation Trust, London, UK; and [4]Division of Pediatric Nephrology, Children's Mercy Hospital, Kansas City, Missouri, USA

Optimal fluid removal on peritoneal dialysis (PD) requires removal of water coupled with sodium, which is predominantly achieved via the small pores in the peritoneal membrane. On the other hand, free-water transport takes place through aquaporin-1 channels, but leads to sodium retention and over hydration. PD prescription can be adapted to promote small pore transport to achieve improved sodium and fluid management. Both adequate dwell volume and dwell time are required for small pore transport. The dwell volume determines the amount of "wetted" peritoneal membrane being increased in the supine position and optimized at dwell volumes of approximately 1400 ml/m^2. Diffusion across the recruited small pores is time-dependent, favored by a long dwell time, and driven by the transmembrane solute gradient. According to the 3-pore model of conventional PD, sodium removal primarily occurs via convection. The clinical application of these principles is essential for optimal performance of PD and has resulted in a new approach to the automated PD prescription: adapted automated PD. In adapted automated PD, sequential short- and longer-dwell exchanges, with small and large dwell volumes, respectively, are used. A crossover trial in adults and a pilot study in children suggests that sodium and fluid removal are increased by adapted automated PD, leading to improved blood pressure control when compared with conventional PD. These findings are not explained by the current 3-pore model of peritoneal permeability and require further prospective crossover studies in adults and children for validation.

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Correspondence: *M. Fischbach, Service de Pédiatrie 1, Centre Hospitalier Universitaire Hautepierre, Avenue Molière, 67098 Strasbourg Cedex, France. E-mail: Michel.Fischbach@chru-strasbourg.fr*

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Volume control is increasingly recognized as a major determinant of dialysis adequacy.[1] Indeed, during the last decade, the definition of peritoneal dialysis (PD) adequacy based on solute removal parameters such as urea kinetics (Kt/V) alone has been questioned. Despite increasing the urea dialysis dose by 30%, the morbidity and mortality of adult patients on chronic PD has not improved.[2,3] In contrast, fluid status and the capacity for fluid removal have been shown to predict patient outcome in several studies.[4,5]

Sodium and water retention is common in PD patients: an increased ratio of extracellular water to total water has been documented by bioimpedance spectroscopy in >50% of adult PD patients.[6] Both optimized ultrafiltration and optimized dialytic sodium removal are together associated with a reduction in patient mortality.[7,8] Whereas hypervolemia in patients on PD is primarily the result of the loss of residual renal function, it is also correlated with peritoneal membrane permeability for solutes such as glucose and sodium.[6]

The achieved ultrafiltration (UF) is determined from the balance between the delivered and the drained dialysate and is used as a clinical definition of the dialytic water balance.[1] Importantly, dialytic sodium removal (DSR) should be measured rather than estimated from the achieved UF,[9] as the DSR is the result of peritoneal absorption (composed of direct lymphatic absorption and absorption into interstitial tissues, such as the peritoneal membrane), and primarily convective transport, with a small contribution of diffusive mass transport.[1,10,11] The DSR also changes with modification of dietary sodium intake and is not strictly correlated with changes in UF.[12] This dynamic, dissociated process of PD water and sodium transport limits the accuracy of estimating sodium transport from fluid removal.

To optimize the PD prescription in terms of sodium and fluid management, it is important for clinicians to understand the impact of varying dwell time and dwell volume on the DSR,[13] and to have a working knowledge of the 3-pore model of peritoneal membrane transport. The principles of dialytic water balance and how varying dwell time and dwell volume influence it is discussed extensively in other reviews.[1,11,13]

The 3-pore model: clinical application

The physiology of water and solute transport across the peritoneal membrane during PD is well described by the

3-pore model.[14] There are 3 types of pores, and their number is inversely related to their size. The ultrasmall pores, also known as endothelial aquaporin-1 (AQP-1) channels, are most abundant and are involved in sodium-free water transport driven by a crystalloid osmotic gradient created by the high dialysate glucose concentrations. The small pores, which are 10,000-fold less abundant than AQP-1 channels, allow both diffusion and convection to take place. The small pores permit small solute transport from blood to dialysate as well as from dialysate to blood. The large pores, which are a million-fold less abundant than AQP-1 channels, facilitate convective mass transport, but also leakage of macromolecules into the peritoneal cavity. Their role in the determination of the total amount of UF is negligible. Their function is increased by inflammation.[1] Finally, the lymphatic route is responsible for fluid, solute, and macromolecular reabsorption.

The small pore function manifests in the permeability of the peritoneal membrane during the peritoneal dialysis exchange, as is routinely analyzed through performance of the peritoneal equilibrium test.[15,16] The small pores facilitate solute-coupled water movement driven by diffusive and convective mass transport. Solute (urea, glucose) removal across the small pores is mainly a diffusive process determined by the number of small pores present in the membrane and recruited by the dwell volume, as well as by the diffusion gradient and the diffusion time (Figure 1).[10,11,13–15] Osmotic conductance drives the transport of free water across the AQP-1 channels and is counteracted by absorption of glucose via the small pores, the latter resulting in a time-dependent loss of the crystalloid osmotic gradient.[1,15,17,18] Hence, it is the glucose diffusive process via the small pores that affects the ability of AQP-1 channels to produce free water. The total UF, and thereby the weight loss achieved in PD, is in turn the sum of free water (AQP-1) and coupled-water (small pore) removal.

The transport process of water and sodium during PD is a dynamic process throughout the dwell. Specifically, the contribution of free water transport to total UF is highest during the early phase of an exchange, whereas small pore–driven UF predominates beyond 60 to 90 minutes, depending on the glucose concentration and individual transporter status.[1] The coefficient of variation of total UF is only 8% applying the 3.86% peritoneal equilibrium test, whereas it has been reported as being close to 50% with the use of 2.27% peritoneal equilibrium test and presumably is highly variable with 1.36% dialysate.[15]

Sodium transport in peritoneal dialysis

The factors contributing to peritoneal sodium transport are less well studied than those that influence peritoneal water transport. Because dialytic sodium removal only involves the small pores (Figure 1), the amount of "wetted peritoneal membrane," the portion of the membrane in contact with dialysate, is exceedingly important in recruiting small pores for DSR. In conventional PD, sodium is primarily transported by convection, by peritoneal absorption, and quantitatively less by diffusion.[19,20] After a 6-hour dwell with a dwell volume of 2 l of 1.36% glucose solution, the fraction of sodium removed attributable to convection is 2-fold higher than that attributable to diffusion, and the sodium absorption into the peritoneal tissue and lymphatics is almost equal to the combined diffusive and convective fractions.[19]

As mentioned, in addition to the volume of dialysate available for diffusion and the number of small pores recruited, additional influential factors consist of the transmembrane osmotic gradient and the diffusion time.[10,11,13–15] The diffusive sodium gradient is related to the plasma and dialysate (NaD) sodium concentrations. The dietary sodium intake is another important determinant of DSR and accounts for its variability.[9–12] Currently, commercially available PD solutions contain NaD of 132 to 134 mmol/l, which is only slightly lower than the normal physiological sodium plasma concentration. This sodium gradient between blood and dialysate is variable over the dwell time, with an initial decrease of the NaD (sodium sieving) due to the transient predominance of free water transfer across the AQP-1 channels, presumably leading to some degree of hemoconcentration. The contribution of free water transport to total ultrafiltration during the first hour of a 3.86% glucose exchange averages 35% to 40% with large interindividual variability,[21] but decreases to 20% after 4 hours due to the absorption of glucose across the peritoneal membrane. Thus, the diffusion time available for solute removal is of importance: a short dwell

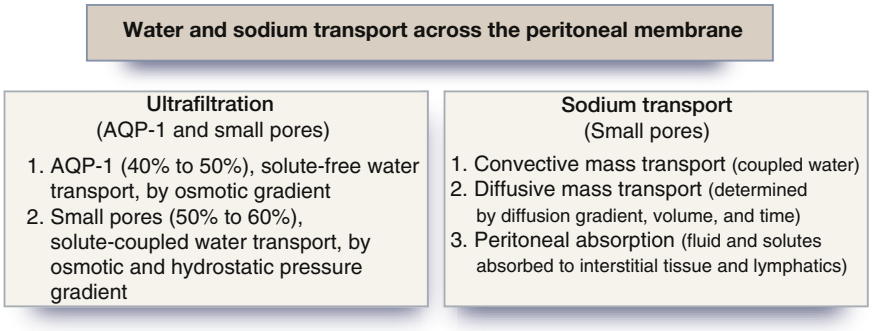

Figure 1 | Peritoneal dialysis permeability for water and sodium: role of aquaporin-1 (AQP-1) channels and small pores.