Peritoneal transport mechanisms and their application during peritoneal dialysis in children

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Peritoneal transport mechanisms and their application during peritoneal dialysis in children

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Part I

General Introduction

1 Peritoneal dialysis in children

Experience with peritoneal dialysis in children has been described for the first time in 1948; it soon became an accepted treatment modality in acute renal failure (1,2,3). However it was not until the introduction of continuous ambulatory peritoneal dialysis (CAPD) in adults by Popovich and Moncrief in 1976 (4), that pediatric nephrologists became interested to apply peritoneal dialysis in end stage renal disease. In CAPD a permanent catheter is surgically or percutaneously implanted into the peritoneal cavity of the patient and is used for the instillation and drainage of the dialysis solution by gravity. This is performed 3 to 5 times per day. CAPD allows children of all ages to receive dialysis at home guaranting a more normal childhood. The technique offers advantages over hemodialysis like the reduced dietary restrictions and the absence of repeated needle punctures. Price and Suki first introduced the use of an automated cycler in pediatric peritoneal dialysis in 1981 (5). In continuous cycling peritoneal dialysis (CCPD) exchanges are performed by a machine instead of manual exchanges based on gravity. The introduction of CCPD was the onset of the development of one of the most popular dialysis regimens used in children: nightly intermittent peritoneal dialysis (NIPD), characterized by approximately 5 to 9 short term dwells during the night, which allows for discontinuation of dialysis during the day. Because dwell times during NIPD are much shorter compared to CAPD, and maximum fluid removal takes place at the beginning of the dwell, NIPD allows more freedom in fluid intake. The empty abdomen during the day also releases the child and his or her parents from worries concerning dialysis.

The development of portable cyclers during the last 5 to 10 years has further improved the quality of life, since treatment is not any longer restricted to a fixed place. In The Netherlands many families have gained excellent experiences with camping holidays since the introduction of the portable cycler. Adaptations to the current cyclers, allowing very small volumes and decreased flow velocities, will also allow very small infants to use a portable cycler.

End stage renal disease is not a common pediatric disorder and as a consequence children account for only a small fraction of the total dialysis patient counts. For example only 2.6% of registered PD patients in the United States were less than 20 years of age in 1996, while 60% of pediatric dialysis patients younger than 15 years were treated with peritoneal dialysis (1). In the Netherlands 58.4% (range 50.9-68.1) of pediatric patients on chronic renal replacement therapy have been treated with peritoneal dialysis during the last decade (1993-2002). Especially in the age group under 13 years peritoneal dialysis is the most popular dialysis modality (data obtained from Renal Replacement Registry Netherlands). (Table 1).

Peritoneal dialysis is the dialysis treatment modality most commonly prescribed for children with end stage renal disease throughout large parts of the world (6). In pediatric peritoneal dialysis only limited studies with respect to the preservation of the stability of the peritoneum are available. This is mainly caused by the relatively short average dialy-

	0 – 2 years		3 - 12 years		13 – 17 years		0 – 17 years	
	PD	HD	PD	HD	PD	HD	PD	HD
1993	71.4	28.6	64.3	35.7	37.5	62.5	54.3	45.7
1994	100	0	70.5	29.5	44.1	55.9	61.4	38.6
1995	100	0	73.3	26.7	58.3	41.7	68.1	31.9
1996	87.5	12.5	55.6	44.4	46.7	53.3	55.4	44.6
1997	75.0	25.0	73.5	26.5	43.5	56.5	62.3	37.7
1998	71.4	28.6	70.6	29.4	42.1	57.9	61.7	38.3
1999	77.8	22.2	61.0	39.0	32.0	68.0	53.3	46.7
2000	55.6	44.4	62.2	37.8	54.3	45.7	58.0	42.0
2001	60.0	40.0	60.0	40.0	57.1	42.9	58.7	41.3
2002	83.3	16.7	56.6	43.5	39.3	60.7	50.9	49.1

Table 1. Ratio peritoneal dialyis (PD) – hemodialysis (HD) in children in The Netherlands.

sis periods in this patient category (7). On the other hand, the relatively low morbidity and mortality rates did not act as driving forces for this kind of studies. It should be remembered however, that although most children on dialysis are the recipients of a renal transplant, sooner or later the subsequent transplant failure will necessitate resumption of dialysis and therefore require the prolonged functionality of the peritoneal membrane as a dialyzing membrane.

Studies on transport kinetics in adult patients have been standardized since the introduction of the peritoneal equilibration test (PET) as prescribed by Twardowski (8). Standard dwell volumes of 2 L are generally used, regardless of the patient's size. Nevertheless comparison of studies on transport kinetics in children with the adult data was hard to make since different intraperitoneal volumes were used. Some studies used intraperitoneal volumes scaled to body weight (9,10), body surface area (11) or both (12,13). Based on recent studies consensus has been reached that PET should be performed with a volume calculated according to body surface area, since the body surface area is roughly proportional to the surface area of the peritoneal membrane (14). De Boer et al. demonstrated an age-independency across the pediatric age range for peritoneal membrane transport parameters if transport parameters were evaluated with a test volume related to body surface area (15). Several studies have confirmed this (11,16,17). Bouts et al. also demonstrated that no differences are found in peritoneal fluid and solute transport characteristics between children and adults when results are corrected for body surface area (17).

As mentioned previously there is only limited knowledge of the long-term functionality of the pediatric peritoneal membrane. The results of some long-term follow-up studies performed in children all suggest that there is no effect of time on peritoneal dialysis on the transport parameters, suggesting a transport stability of the pediatric peritoneal perme-

ability (6,16,17, 18). It should be remembered again, that treatment periods in pediatric peritoneal dialysis are relatively short. Reports on the influence of peritonitis are contradictory. Hölttä et al (16) saw no change of peritoneal membrane function after episodes of peritonitis, while Warady et al (6) reported a trend toward an increase in transport capacity for solutes, like glucose and creatinine. Also Andreoli et al. concluded that children with a history of peritonitis have a peritoneal membrane that is more permeable to glucose and creatinine. Consequently the osmotic gradient will dissipate faster, which could eventually contribute to ultrafiltration failure (19). With respect to the influence of peritonitis episodes in adults there also are conflicting reports in this field. Where one group observed recurrent peritonitis giving rise to an increase in solute transport (20), the other did not see a significant influence on solute transport or fluid kinetics (21).

2 The peritoneal membrane

During the evolution of species, the peritoneal cavity lost its original function as an excretory organ, but with the insertion of an appropriate catheter into the peritoneal cavity we are able to restore this excretory function (22). In peritoneal dialysis a biological membrane lining the peritoneal cavity, the peritoneal membrane, is used to remove uremic toxins and water from the patient. The peritoneal membrane is composed of three different compartments: vasculature, interstitium and mesothelium, each composed of different types of cells: endothelial cells in the capillary walls, fibroblasts in the interstitium and mesothelial cells in the mesothelium.

2.1 The mesothelium

It is generally believed that the mesothelium is not an important barrier to solute transport since there was no osmotic pressure gradient found across it during peritoneal dialysis in rats (23,24) as was investigated by measuring the hydrostatic pressure profiles in the abdominal wall during conditions of isotonicity and hypertonicity. However the mesothelial layer was shown to have a sophisticated junctional complex, a carpet of microvillous projections at the free surface and a cytoplasm replete with organelles (22) and must be considered having the properties of an epithelium with a selective barrier of permeability (25). Also the existence of facilitative glucose transporters in mesothelial cells has been demonstrated (26). This suggests that the mesothelial cells could participate in the osmotic barrier during peritoneal dialysis by conditioning glucose transcellular transport, or by diffusion mediated by glucose transport or even by regulation of solute and water fluxes through tight junction modulation (25). However in vivo transport experiments performed in rats showed that the removal of the mesothelium does not result in a marked enhancement of transport of fluid and small solutes and thus supports the idea that the mesothelium is not a rate-limiting barrier (27).

2.2 The interstitium

The interstitial space between the peritoneal vasculature and cells like parenchymal cells and fibroblasts is filled with extracellular matrix. This extracellular matrix gives the tissue

its mechanical and physicochemical properties and acts as a framework for cell attachment and migration (28). Hyaluronan, a soluble glycosaminoglycan, is a major component of the extracellular matrix (29). This polysaccharide is found in all tissues and body fluids and participates in fluid homeostasis, response to inflammation and wound healing (29,30). Increasing evidence suggests that the hyaluronan content in the interstitium is one of the major determinants of the resistance to transperitoneal transport of water and solutes (23, 31–34). Hyaluronan seems to increase the diffusion coefficient for solutes (35) and seems to exert effect on the hydraulic conductivity of tissues involved (33,34). However it is still poorly understood how hyaluronan acts within the tissue to modulate transport (34, 36). In chronic peritoneal dialysis it is possible that the peritoneal membrane content of hyaluronan is reduced, since hyaluronan may be washed out, thereby increasing the interstitial hydraulic conductivity (37). Recent studies suggest that intraperitoneally administered hyaluronan (added to the dialysis fluid), improves the efficiency of ultrafiltration during peritoneal dialysis by reducing the peritoneal fluid back-filtration. This effect is dependent both on molecular weight and concentration of hyaluronan (38,39) and is thought to be the result of the impact of hyaluronan exerted on the peritoneal surface area. When added repeatedly to the peritoneal dialysis fluid during a longer period, hyaluronan seems to affect the hydraulic conductivity of the interstitium: the increase in peritoneal solute transport rate, caused by repeated exposure to hypertonic glucose solutions was prevented in a group of Sprague-Dawley rats after repeated intraperitoneal use of hyaluronan (40).

2.3 The capillary wall

The peritoneal capillary wall is generally assumed to be the main barrier to transperitoneal transport of solutes in peritoneal dialysis. The capillaries of both the parietal and the visceral peritoneum are mainly of the continuous type, but 1.7% of the capillaries have been reported to be fenestrated (41). The fenestrae in these capillaries have been suggested to be the ultrastructural equivalent of the large pores, which represent a non-size-selective pathway for macromolecules. However the size of the fenestral openings is too large (60-90 nm) to be considered the structural equivalent of the hypothetical large pores (radii of 11-35 nm) and the density of these pores is substantially lower than the density of fenestrae (42).

Tight junctions link the capillary endothelial cells to each other. These tight junctions consist of protein molecules such as occludin and cadherin (43,44). Especially occludin creates a barrier to diffusion of solutes (43). The tight junctions are probably the equivalent of the small pore system.

During the last decade the presence of aquaporin-1, a transmembrane water channel protein, was demonstrated in the endothelial cell surface of peritoneal capillaries (45–,47). Recently the expression of aquaporin-1 was also demonstrated in human peritoneal mesothelial cells (48) and in rat peritoneal venular endothelial cells (49). Although ten different aquaporins have been identified in man, several studies make it likely that aquaporin-1 is the chief candidate to represent the ultrasmall-pore system (49–51).

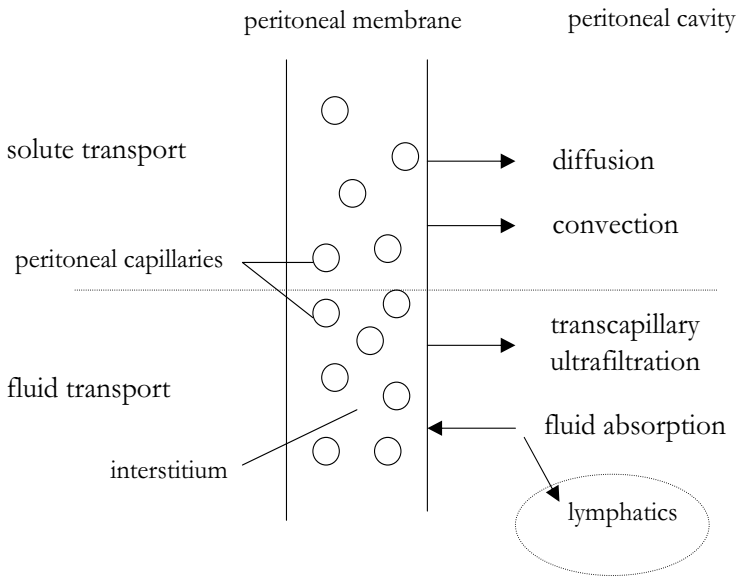

Figure 1. Routes for peritoneal transport of solutes and fluid. Solute transport occurs by either diffusion or convection. Fluid transport occurs by either osmotic or oncotic induced transcapillary ultrafiltration or by absorption out of the peritoneal cavity directly into the peritoneum or via the lymphatic vessels.

3 Peritoneal solute and fluid transport

The biological character of the membrane used in peritoneal dialysis, requires a good understanding of the transport pathways in order to achieve an appropriate dose of dialysis for every individual patient. Despite of extensive studies on the kinetics of solute and fluid removal from the peritoneal cavity during peritoneal dialysis, our understanding of transperitoneal transport is still not complete.

Figure 1 summarizes the current understanding of the routes for peritoneal solute and fluid transport. The changes in intraperitoneal volume during peritoneal dialysis are the result of fluid transport from the blood to the peritoneal cavity, and the removal of fluid out of the peritoneal cavity.

3.1 Transport into the peritoneal cavity

For transport of fluid from the blood to the peritoneal cavity, osmotic and oncotic induced ultrafiltration plays an important role (see paragraph 3.3). Removal of uremic toxins across the peritoneal membrane occurs by two major mechanisms: diffusion and convection (35, 52, 53). Diffusion is the most important transport mechanism for low molecular weight solutes, and occurs bi-directional depending on the concentration gradient between blood and the dialysis fluid in the peritoneal cavity. The product of the mass transfer area coefficient (MTAC; the maximum theoretical clearance by diffusion at time zero, when no

transport has taken place yet) and the concentration gradient between blood and dialysis solution determines the rate of diffusion (35). Diffusion is a size-selective process, which means that small molecules diffuse at a faster rate than larger molecules, due to differences in their free diffusion coefficient (53).

Convective transport of solutes occurs when equilibrium is present between plasma and the dialysis fluid. Transport of solutes is then determined by the net water transport between plasma and dialysate. The rate of convective transport is limited by two factors: 1) solute sieving and 2) fluid absorption from the peritoneal cavity. The sieving of solutes is determined by the ratio between the dialysate concentration of a solute and its plasma concentration when no transport by diffusion occurs. It can range between 0 (no convective transport at all) and 1.0 (the membrane does not hinder convective transport) (35).

3.2 Transport out of the peritoneal cavity

During peritoneal dialysis, fluid is lost from the peritoneal cavity into the tissues surrounding the peritoneal cavity and via the lymphatic vessels. The hydraulic pressure within the peritoneal cavity mainly determines the loss of fluid from the peritoneal cavity, which is in contrast with the crystalloid osmotic and colloid osmotic driven transport into the peritoneal cavity (54). A hydrostatic driven flux of fluid and solutes occurs into the tissues surrounding the peritoneal cavity, subsequently followed by absorption into the intratissue lymphatics (54). Besides this hydrostatic pressure driven transport, fluid is also transported from the peritoneal cavity by subdiaphragmatic lymphatics. The lymphatic openings, also called stomata, permit absorption of intraperitoneal particles, cells, colloids and fluid (55). This lymphatic absorption takes place as a result of excursions of the diaphragm during respiration. The majority of investigators agree that fluid absorption directly into the tissues surrounding the peritoneal cavity is the predominant way governing fluid loss from the peritoneal cavity (54).

Based on our current knowledge of peritoneal transport mechanisms there remains difficulty in understanding how fluid absorption into peritoneal tissues and transperitoneal ultrafiltration can occur at the same time. Based on the knowledge that during a normal dwell only a fraction of the anatomical surface area of the peritoneal membrane comes in contact with the dialysis solution (56), Leypoldt suggested that a small amount of fluid will permeate regions of the peritoneum that are not in contact with dialysate, where the fluid will lose its osmotic solutes and will be absorbed due to the hydraulic pressure in the peritoneal cavity (52).

Several studies concerning peritoneal fluid kinetics refer to the amount of fluid loss from the peritoneal cavity using the term ‘lymphatic absorption rate’. Since the disappearance of a marker is used to measure fluid loss from the peritoneal cavity (both into the surrounding tissues and by subdiaphragmatic lymphatics) we prefer to use the term marker clearance instead of lymphatic absorption.

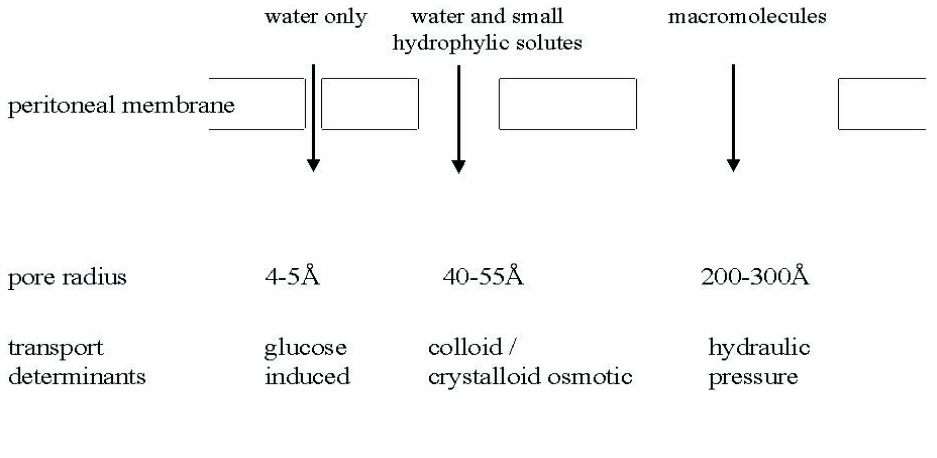

Figure 2. Three-pore model of peritoneal transport of solutes and water

3.3 The three-pore model

Although quite simple, the "three-pore model" developed by Rippe et al is still the most applied mathematical approach of the intraperitoneal volume versus time relationships under various conditions in peritoneal dialysis (57–60). This computer model only takes into account the transport barrier of peritoneal capillary wall and neglects the mesothelium and the interstitium. Several other published models also take into account the interstitium and the mesothelium, but even though they are more accurate in describing transperitoneal transport (61,62) their complexity refrains them from being used (59).

According to the three-pore model the peritoneum behaves as a membrane having three different types of functional pores: the water-exclusive aquaporins, the small-pore pathways and the large-pore pathways (Figure 2). The frequencies of the pores are inversely related to their pore sizes. Thus there are approximately 10^6 aquaporins and 10^4 small pores on every large pore (63).

The small pores represent the major exchange pathway for small hydrophylic solutes and for water (58). Fluid transport is determined by crystalloid and colloid osmotic pressures. The crystalloid osmotic pressure gradient during peritoneal dialysis with conventional solutions is determined mainly by glucose (35). Its effectiveness as an osmotic agent depends on the resistance the membrane exerts to glucose transport. This is expressed as the osmotic reflection coefficient, σ (35). It can range from 1 (no passage, ideal semipermeable membrane) to 0 (passage not hindered). A value of 0.03 for glucose has been calculated in CAPD patients (64).

The large pores allow for a slow, unidirectional flux of macromolecules and fluid from blood to the peritoneal cavity. This transport is driven by hydraulic forces (57–59,64). Computer modeling according to a two-pore formalism of peritoneal transport (taking into account transport across the large and the small pores) allowed for calculation of the

individual contribution of each pore system. The large pores are likely to contribute 5 to 6% to transcapillary ultrafiltration (59). Colloid osmotic forces are negligible across this pore system (65).

The existence of a third pathway was postulated to be a water-only pathway that rejects solute transport (57–59). Computer simulations of peritoneal transport revealed that this water-only pathway allows for nearly one half of the ultrafiltration using conventional glucose solutions (57). This was confirmed in an *in vivo* study (66). The reflection coefficient of glucose will approach 1.0 across these ultrasmall pores, which might explain why glucose is such an effective osmotic agent despite its small size (35).

4 Methods to evaluate peritoneal transport characteristics

The most widely used approach to evaluate peritoneal transport characteristics in individual patients is the performance of a Peritoneal Equilibration Test (PET) in order to measure the dialysate to plasma solute concentration ratio (D/P) for small solutes and the dialysate to initial dialysate glucose concentration ratio (D_t/D_0) during a 4-hour dwell period with a conventional peritoneal dialysis fluid. Based on reference values, the transporter state of an individual can be characterized as high, high average, low average or low (8). The disadvantage of the D/P ratio is that it is dependent on the volume used: using a smaller test volume will result in a higher D/P ratio, reflecting a more rapid equilibration of the solute between dialysate and plasma but not necessarily enhanced transport capacity (40). This is explained by the fact that equilibration occurs more rapidly when the dialyzed solute diffuses into a relatively small volume. The MTAC characterizes the diffusive permeability of the peritoneal membrane independent on dialysis mechanics. Therefore it is better to use the MTAC for low molecular weight solutes if you want to compare solute transport data in study groups using different test volumes.

Adaptation of the PET allows for calculation of more useful and extensive information on transport parameters of the peritoneal membrane. The addition of poly-disperse dextran 70 to the test solution allows for the simultaneous measurement of transcapillary ultrafiltration, marker clearance rate, and intraperitoneal volume. Both in adults and in children experiences with this modified PET, also called a standard permeability analysis (SPA), have been reported.

Reddingius et al performed PETs in children, using a test volume of 1200 ml/m² and 1.36% glucose and 3.86% glucose as a test solution (67). They compared the results with those obtained in adult patients and did not find any differences. Bouts et al used a 1.36% glucose solution as a test solution and also did not find essential differences between adults and children (17).

Studies performed in adult patients revealed that it is best to perform a peritoneal function test with a 3.86% glucose solution because it provides better information on ultrafiltration as compared to glucose solutions with lower glucose concentrations (68,69). Solutions with a higher osmolarity will provide more information on transcellular water transport than those with a low hyperosmolarity (like 1.36% glucose solution) since the latter will

hardly induce transcellular water transport (68). It was demonstrated that the use of test solutions with different osmolarities do not affect solute kinetics, lymphatic absorption and the contribution of small pores to peritoneal transport (68).

Haraldsson was the first to describe the use of the Personal Dialysis Capacity test (PDC) as a method of estimating the true peritoneal capacities of individual patients (70). This method is based on the three-pore model of fluid and solute transport across the peritoneal membrane and was designed to mimic an ordinary dialysis day. The PDC is performed by the patient him/herself, following a protocol with 5 exchanges in 24 hours using different dwell times and two different glucose solutions. The PDC is used to calculate 3 parameters: 1) the 'area parameter' or unrestricted pore area available for exchange over the diffusion area ($A_0/\Delta X$), which is a fundamental physicochemical parameter for transport across porous membranes, determining the diffusion capacities for all solutes, 2) 'absorption' or the reabsorption rate of fluid from the abdominal cavity to blood, when the glucose gradient has dissipated and 3) the 'large pore flow' representing the flux of plasma through the large pores (70). In a large multicentre trial it was confirmed that the PDC is a reliable tool for routine evaluation of the peritoneal membrane (71). Thus far only one study was undertaken to evaluate the effectiveness of PET and PDC in estimating the peritoneal exchange capacity in comparison to one another. It was demonstrated that the unrestricted pore area available for exchange over the diffusion area correlated much better to the plasma appearance rate of intraperitoneally administered iohexol than the PET parameters (72). As iohexol has proven to be a useful marker of the peritoneal exchange, or the capillary exchange of solutes during dialysis (73), this study implies that $A_0/\Delta X$ is a better indicator of peritoneal membrane function than PET parameters are (72). In children limited experience with PDC has been published. Schaefer et al confirmed that the PDC test is able to model the individual peritoneal membrane function with precision (74). They showed that the test could also be performed in APD patients using a simplified study protocol, not requiring a change from an APD to a CAPD regimen, without losing its precision and reliability. This facilitates the use of a PDC test in most pediatric patients (74). More recent data obtained in pediatric patients imply that $A_0/\Delta X$ can be estimated adequately from the D/P ratios derived from PET analysis (63). In this study experimentally determined D/P or D/D_0 concentration ratios for urea, creatinine, phosphate, protein and glucose were used to estimate $A_0/\Delta X$ for each individual patient by using newly developed computer software (63). This implies that routine performance of PET, in combination with the use of adapted computer software will be sufficient to evaluate peritoneal membrane function with more precision.

5 Adequacy of peritoneal dialysis

There is an increasing recognition of the influence of adequate solute clearance on patient outcome in peritoneal dialysis. Studies in adults have suggested that higher clearances of small molecules are associated with better survival and lower morbidity (75). As a consequence measurement of peritoneal dialysis efficiency is based on the clearance of small

solutes like urea and creatinine.

Current standards suggest the use of a full 24-hour dialysate collection to estimate precisely the creatinine clearance (CCr) and the Kt/V urea in automated peritoneal dialysis (76,77). A CCr of 63 l/week/1.73 m² and a Kt/V urea of 2.1 have been proposed as adequacy targets for a CCPD regimen and a CCr of 66 l/week/1.73 m² and a Kt/V urea of 2.2 for a NIPD regimen (78). The differences in adequacy targets between the different dialysis regimens are based on the fact that there is an 8% difference in clearance between CAPD and NIPD, suggesting that the delivered dose of NIPD would need to be 8% higher than the CAPD dose. Subsequently it is assumed that the required dose of CCPD would need to be intermediate between those for CAPD and NIPD (78). For children similar figures have been proposed (79). However it is generally accepted that a CCr > 63 l/week/1.73 m² is very hard to achieve (7,80,81), especially in anuric patients.

In adult patients mortality is often used as a criterion for dialysis adequacy (82), but it is harder to define adequate dialysis in children. Schaefer et al (7) stated that the peritoneal transport state is a weak but significant independent determinant of growth and body mass acquisition: high transporters were found to be at increased risk for growing poorly and becoming obese. Also hospitalization time, metabolic control and the need for medication are suggested as measures for clinical outcome (80). The sparse data in pediatric patients suggest an improvement of clinical outcome under adequacy control (7,80), however the number of patients studied and the limited follow-up period in the studies concerned do not provide definitive evidence. A recent study underlines the importance of critical judgment of the use of adequacy control based on creatinine and urea kinetics (83). In a prospective randomized study in 965 adult patients it was shown that increases in clearances of urea and creatinine did have no effect on patient survival at all. These sensational and unexpected results presently give rise to reflection in the peritoneal dialysis world (84–90).

Beside the use of CCr and Kt/V urea as index of dialysis adequacy, also the use of the solute removal index (SRI) has been suggested. The SRI is also based on solute removal, but it normalizes removal by the solute content of the body at the beginning of the treatment or at the beginning of the week: the ratio between net urea removal and the predialysis urea body pool is determined (91,92). The SRI appeared to be a more reliable index of adequacy compared to Kt/V urea in children, since most children are on an intermittent dialysis regimen and SRI is independent of the time that the clearance of solutes (or dialysis) is applied (93). Further studies will be needed to further explore the usefulness of SRI as a tool to measure dialysis adequacy.

Efficiency measurement based on creatinine and urea kinetics does not take into account the clearance of low molecular weight plasma proteins and the so-called 'middle molecules', with a molecular weight ranging from 0.3-5 kD. Montini et al demonstrated in pediatric patients that there is a progressively increasing peritoneal resistance to the transport of substances with increasing molecular weight (especially when the molecular weight is ≥ 5 kDa) (94). Another study reported an increase of the restriction coefficient for macromolecules

in relation to time on peritoneal dialysis, which indicates an increased size selectivity or a reduced peritoneal permeability for higher molecular weight solutes (17). The residual renal function seems to play a central role in removing some low molecular weight plasma proteins and the 'middle molecules' (94). As a consequence patients on peritoneal dialysis will have greater difficulty removing higher molecular weight substances and therefore accumulation of many substances will occur, especially in patients with no residual renal function. A study in adult patients also showed that as solute molecular weight increases the influence of decreased daily dialysis time becomes increasingly important (95). Especially in children, who often are on a nightly intermittent peritoneal dialysis (NIPD) regimen with relatively short dwell times, this seems to be of significance.

One of the low molecular weight plasma proteins that seem to accumulate in patients on PD is leptin. Leptin is a product of fat cells that regulates food intake through modulation of satiety signals (96). Recently elevated levels of leptin have been reported in adult and pediatric uremic patients, especially in those treated with peritoneal dialysis (97–99). In children an inverse relationship was observed between body mass index-adjusted leptin levels and the spontaneous energy intake, which supports the hypothesis that inappropriate elevated levels of leptin contribute to decreased nutrient intake (97).

6 Changes in peritoneal permeability

As discussed previously diffusion is the most important transport parameter for low molecular weight solutes. The product of the mass transfer area coefficient and the concentration gradient between blood and dialysis fluid determines the rate of diffusion. The MTAC is mainly determined by the so-called effective peritoneal surface area, or functional area of exchanges between blood and dialysate.

The effective peritoneal surface area is determined by two parameters: the amount of perfused peritoneal capillaries and the size of the contact area between the peritoneum and the intraperitoneal dialysis solutions. Consequently changes in the capillaries, in the amount of perfused capillaries and in the size of contact area between the peritoneum and dialysis solutions will affect the peritoneal permeability.

6.1 Changes in vascular surface area

6.1.1 Nitric oxide

Several lines of evidence suggest that nitric oxide (NO) is involved in regulation of peritoneal transport during peritoneal dialysis. NO is synthesized from L-arginine by a family of 3 NO synthase (NOS) isozymes, according to the tissue in which they were initially cloned: neuronal NOS , inducible NOS (cloned from macrophages) and endothelial NOS (eNOS). Addition of the NO donor nitroprusside to the dialysate increases both the effective peritoneal surface area and the intrinsic permeability of the membrane in animal models (100) and PD patients (101). Long-term PD is associated with a progressive increase of NOS activity within the peritoneum, due to upregulation of eNOS, which reflects

neoangiogenesis (102). There was a strong positive correlation between time on PD and increase in NOS activity (102). The development of a large vascular peritoneal surface area was already suggested by the high solute transport rates that have been described in long-term peritoneal dialysis patients (103,104) and confirmed by histomorphometric studies (102,105). In a rat model of acute peritonitis an increase of NOS activity was seen due to upregulation of eNOS and iNOS (106).

6.1.2 Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a heparin-binding growth factor that plays a prominent role in physiologic and pathologic angiogenesis (107). As demonstrated in a rat model, VEGF is a key mediator in hyperglycemia-induced neoangiogenesis (108,109) and also seems to be responsible for inducing and maintaining the baseline permeability of the endothelial cells (108). In long-term peritoneal dialysis patients there is a marked upregulation of the expression of VEGF (102). In the human peritoneal membrane VEGF is localized in the endothelium lining the peritoneal capillaries (102). The amount of VEGF present in fresh peritoneal effluent suggests local production of VEGF in addition to unknown amounts potentially transported from plasma (110, 111). Relations between peritoneal transport parameters and peritoneal effluent VEGF levels were found by Zweers et al (110) but could not be confirmed by others (111). There was a lack of correlation between VEGF levels and cumulative glucose exposure (111). Recently it was demonstrated in rats that octreotide, a long-acting somatostatin analog, is able to protect against vascular alterations and preserving peritoneal function by inhibiting overexpression of VEGF (109). Although it is clear that VEGF plays a role in peritoneal angiogenesis, it is likely that VEGF is integrated in a complex relationship involving multiple peritoneal structures and growth factors (102,107, 111, 112).

6.1.3 Advanced glycation end products

Advanced glycosylation end products (AGEs) are formed as the result of the non-enzymatic glycosylation of proteins (113). The AGEs that are formed from this reaction can irreversibly accumulate on long-lived proteins. Glucose degradation products (GDPs), like glyoxal, methylglyoxal and 3-deoxyglucosone induce the advanced glycation of proteins. Figure 3 summarizes the chemical reactions leading to the formation of GDPs. Patients on peritoneal dialysis are exposed to high concentrations of these GDPs: they are exposed to GDPs that originate from the uremic circulation (114–116) and from the glucose-based dialysis fluids in which glucose is converted into GDPs during heat sterilization. Consequently there is accumulation of AGEs within the peritoneal membrane (102,112). Peritoneal AGE accumulation increases with time on peritoneal dialysis: both prolonged use of glucose-containing dialysis solutions and more frequent use of glucose solutions with a higher glucose concentration result in higher peritoneal AGE accumulation (117). Peritoneal AGE accumulation also increases with increasing number of peritonitis episodes (117). This might be a consequence of the increased glucose load during peritonitis, used to overcome smaller ultrafiltration volumes (22).

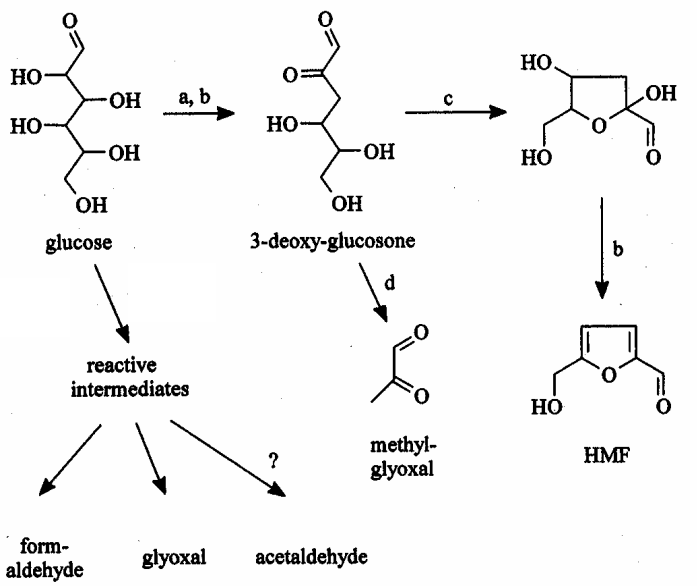

Figure 3. Formation of certain glucose degradation products via (a) enolization, (b) dehydration, (c) cyclization and (d) C-C-cleavage

6.2 Changes in the effective peritoneal surface area

In animal studies it was demonstrated that even with the use of large intraperitoneal volumes the area of contact between dialysis fluid and the peritoneal membrane is limited to approximately 25-30% of the total peritoneal area (56, 118, 119). Determination of the proportion of the peritoneal surface area in contact with the dialysis fluid was performed by addition of labeled IgG to a dialysis solution and subsequent analysis of the peritoneum of the animal (56). The contact area of a dialysis fluid in the peritoneal cavity was 0.55 m^2 in 6 patients (120), implying that 30 to 60% of the anatomic area is wetted during peritoneal dialysis in a 70 to 80 kg patient, using a fill volume of 2 L (56). Increasing the effective peritoneal surface area improves the mass transfer of small solutes and thus the efficiency of dialysis (56,118,119,121−123). There are several methods of enhancing the effective peritoneal surface area like increasing the intraperitoneal fill volume, adjustment of posture and the use of surfactants. In mice it was shown that when given enough time in the peritoneal cavity, the fluid would make contact with most of the peritoneal surface (56), presumably through the peristaltic movement of the hollow viscera. It is not likely that this slow movement of fluid through the cavity will increase the contact area through which the transfer of solutes will occur. The violent maneuvers imposed in animals, that actually did affect the mass transfer (117,118) are not practical or ethically justified in human beings. However the application of low-frequency vibration to the abdominal wall for three 20-minutes periods every day also has a considerable effect (124).

Both in adults and children the fill volume affects the effective peritoneal surface area (63, 125). For children the 'maximum' area available for exchange is obtained at a fill volume

of 1400 mL/m² body surface area (63). Also posture has considerable effects. Both in adults (126,127) and children (128) the mass transfer of small solutes fell in the standing position compared with the supine position. In 6 children the effective peritoneal surface area decreased with 25% with the patient in the standing position (63).

The addition of surfactant to dialysis fluids might be another possibility of contact area enhancement. Dioctyl sodium sulfosuccinate (DSS) increases the mass transfer of small solutes in a dose-dependent way (121–123,129) in animal models. Before human implementation of the use of DSS as a surfactant, extensive studies are needed to further investigate toxicity, inflammatory effects and the increased loss of proteins (56,122). The addition of hyaluronan to dialysis fluid also leads to changes in peritoneal permeability as a result of changes in the hydraulic conductivity of the peritoneal membrane, leading to higher net ultrafiltration (30). This was already discussed in an earlier paragraph. Again extensive studies will be necessary before human implementation.

As DSS is able to restore ultrafiltration by increasing the effective area of contact between dialysate and the peritoneal membrane, the addition of surface-active phospholipids (SAPL) seems to restore ultrafiltration by restoration of membrane semipermeability (130). Adsorption of SAPL to peritoneal mesothelium replenishes deficient lining. Currently some clinical trials are running, examining the effect of intraperitoneal administration of a synthetic SAPL. The great advantage of the use of synthetic SAPL is, that it has already been used for two decades in the treatment of acute respiratory distress in newborns and has proven to be completely safe (130).

7 Innovations in peritoneal dialysis solutions

As a result of the growing awareness of the potential effects of the glucose-based, lactate buffered solutions on peritoneal membrane physiology, there is an increasing interest in development of more biocompatible dialysis solutions. In spite of all research, glucose is still the most widely used osmotic agent in peritoneal dialysis fluids. Glucose has proven to be effective and inexpensive, but evidence is growing that continuous exposure to high intraperitoneal glucose concentrations has detrimental effects on the peritoneal membrane. The high glucose concentrations depress proliferation and cytokine production of mesothelial cells (131,132). Also the deposition of AGE in the peritoneal membrane (112, 133) and the findings of advanced vascular changes typical of diabetes in peritoneal biopsy samples (105, 134, 135) are related to the long-term use of high glucose concentrations. The goal for the clinician is to avoid the pathogenic factors, which are responsible for changes in the peritoneal membrane. These factors are: (*1*) a low pH and lactate and glucose itself, through its metabolism via the polyol pathway (136); (*2*) glucose exposure leading to vascular changes of neovascularisation and deposition of type IV collagen in the interstitium (105); (*3*) formation of advanced glycation end products in peritoneal tissue (137,138) and (*4*) the presence of glucose degradation products generated during steam sterilization (137,138,139).

The greater appreciation of the deleterious effect of current solutions has led to the development of a large number of solutions that differ either in buffer, sterilization procedure or composition.

7.1 Bicarbonate-buffered dialysis fluid

Bicarbonate-based PD solutions are buffered at neutral pH. The use of this more physiological buffer can be achieved only if a double bag is created: one side containing glucose and calcium, the other containing sodium bicarbonate. These bags have to be mixed shortly before administration. Bicarbonate-buffered solutions have a more physiological pH (7.0-7.6) than lactate-based solutions (pH 5.5-6.5) (140). The solutions currently available are entirely bicarbonate or a lactate/bicarbonate mixture. *In vitro* studies showed markedly better preservation of the function of macrophages and peritoneal mesothelial cells (141,142). Evidence is not yet available that bicarbonate solutions impart benefit to patients in terms of preserving the peritoneal membrane integrity. Clinical experience in pediatric patients has been presented, showing no differences in peritoneal mass transport kinetics between bicarbonate and lactate buffered solutions for water and most solutes (143, 144). In the PET in pediatric patients both solutions also have similar behavior (145). The results of a comparative study between the conventional lactate-buffered and the new bicarbonate-buffered solution performed in children suggest that the bicarbonate -buffered solution has a superior clinical tolerance (146). Less inflow pain induced a lower intraperitoneal pressure, and a lower unrestricted pore area available for exchange over the diffusion area ($A_0/\Delta X$) suggesting the occurrence of fewer long-term vaso-active effects of the bicarbonate buffered dialysis fluid. As these results were obtained from a very short-term study, long-term clinical trials will be needed to confirm the idea that bicarbonate buffered dialysis fluids will improve dialysis therapy for children on cchronic peritoneal dialysis. Patients who experience pain at infusion of PD fluid related to pH and lactate have been shown to improve dramatically on bicarbonate and bicarbonate/lactate solutions (142,147).

7.2 Double chambered bags

Acetaldehyde is detected as a major glucose degradation product in single-chamber peritoneal dialysis fluid bags. Acetaldehyde is formed during heat sterilization, by a mechanism that is mediated by glucose (136). Consequently separation of glucose and lactate during heat sterilization by the use of a double-chamber bag inhibits the formation of acetaldehyde (136). Separation of glucose from other solution components also allows for glucose to be sterilized at a lower pH than is possible in single-chamber bags. It has been shown that the low pH in the glucose compartment (especially in a pH range between 2.5 and 3.5) considerably lowers glucose degradation (136). Until now there have been no biological function data or clinical outcome studies supporting the idea that double-chamber bags are superior to single-chamber bags. However glucose degradation products are known to be a precursor of AGEs, which implies that double-chamber bags with low glucose degradation products levels will be favorable to peritoneal membrane integrity.

7.3 Icodextrin

Icodextrin is mainly characterized by the absence of glucose. Instead long-chain glucose polymers are present which are responsible for the ultrafiltration. The commercially available 7.5% glucose polymer solution, icodextrin, contains a polydisperse solution of starch derived glucose polymers with a mean molecular weight of 16.800 Da and a pH of 5.2-5.6. Icodextrin is capable of inducing an osmotic flow across the peritoneal membrane, even though the solution is iso-osmolar to plasma (284 mOsm/kg). Ultrafiltration occurs according to the principle of colloid osmosis, meaning that there is a fluid flow across a semipermeable membrane in the direction of the relative excess of large molecules (148).

Extensive long-term clinical experience with icodextrin in adults has been reported (66,149−153). The solution induces a slow but sustained ultrafiltration for up to 16 hours in automated peritoneal dialysis (148,149,153) and the ultrafiltration volume obtained after a long-term dwell is similar to the ultrafiltration volume obtained with a 3.86% glucose solution (149,153). Clinical studies show that icodextrin is especially effective during long-term dwells and in patients with ultrafiltration failure due to a large effective peritoneal surface area (154−157). Also computer modeling suggests that icodextrin will produce an increased ultrafiltration rate in patients with an increased effective vascular surface area (66). Icodextrin has proven to be able to preserve the daytime dwell ultrafiltration during peritonitis, when glucose often fails as osmotic agent due to increased glucose absorption (158) and both fluid and blood pressure control improve with the use of a daytime dwell with icodextrin (159). One study performed in 21 adult patients demonstrated a beneficial effect of icodextrin use on lipid profiles (160), which is one of the major risk factors for cardiovascular complications.

Several studies have been published concerning the side effects of icodextrin. The main side effect of icodextrin use has been skin rashes, which were documented both in adults (161−164) and in children (165). Another side effect of icodextrin use is the occurrence of icodextrin induced sterile peritonitis (166−168). Patients present with cloudy dialysate, no or mild abdominal pain, a variable cell count with a variable percentage of neutrophils, monocytes, eosinophils and lymphocytes, dialysate cultures remain negative, and complaints disappear after discontinuation of icodextrin. For a long time the pathogenesis of these peritonitis episodes was not clear, and hypersensitivity to icodextrin seemed to be the most likely cause. However extensive investigations revealed that the problems are probably due to contamination of some batches of icodextrin with a peptidoglycan, which is a non-endotoxin weak pyrogen capable of provoking inflammatory responses (169). In these cases of sterile peritonitis icodextrin should be stopped. If the effluent becomes clear after discontinuation of icodextrin, it seems worth trying icodextrin from a different batch. But if on icodextrin rechallenge the complaints recur, then icodextrin should not be prescribed again, and hypersensitivity for icodextrin should be considered.

Icodextrin exerts no long-term toxicity. Its use is accompanied with a rise in plasma oligosaccharides, but no clinical adverse events have been related thus far. Oligosaccharide levels return to baseline after ending treatment (151, 165). Several *ex vivo* studies have

demonstrated improvement in both peritoneal and mesothelial cell function in patients using icodextrin-based dialysis solutions for one exchange per day while using conventional solutions for the other exchanges (170,171). In addition the use of icodextrin decreases the formation of advanced glycation end products (172,173), but in combination with nighttime exposure to glucose there is no decrease of effluent levels of glycation end products observed (173). It was also demonstrated that the use of icodextrin is accompanied with a decrease in the effluent concentration of reactive carbonyl compounds (which generate advanced glycation end products) as compared to the conventional heat-sterilized glucose solutions (174). However some doubts about the safety of icodextrin have been raised following the results of an in vivo study in mice suggesting that icodextrin induces substantial DNA injury through a mechanism of lipid peroxidation (175). Also long-term use of icodextrin in rats was shown to induce increases in peritoneal protein excretion, although transport of small solutes was not affected (176). Further studies are needed to elucidate these negative effects of icodextrin in humans.

In contrast with the extensive amount of experiences with icodextrin reported in adult patients, thus far only one study has been published reporting experiences with icodextrin in pediatric patients (165). It was demonstrated that the addition of a daytime icodextrin dwell to a NIPD regimen with conventional glucose solutions results in an increase of ultrafiltration and gives an increase of the weekly Kt/V urea of 0.52. The metabolism of icodextrin is similar to that in adults, implying an increase of serum oligosaccharides maltose, maltotriose and maltotetraose, reaching a steady state level after approximately two weeks and followed by a decrease to baseline levels after stopping treatment. This study also demonstrated that icodextrin is capable of inducing a sustained ultrafiltration for up to 12 hours and the ultrafiltration volume after 12 hours is comparable to the ultrafiltration volume obtained with a 3.86% glucose solution (165). In chapter 1 the effect of icodextrin on solute and fluid kinetics in children will be discussed and a comparison is made with the transport characteristics of icodextrin obtained in adult patients (66).

8 Intraperitoneal drug administration

The main objective during peritoneal dialysis in children is the removal of excess body water and waste products, using the peritoneal membrane as a filter. However once a permanent catheter into the peritoneal cavity is present, it allows for usage of the peritoneal cavity as a pathway of drug application. This administration route can be advantageous in cases of intravenous access problems, treatment of infections or malignancies localized to the peritoneal cavity but it can also be very well applied to treat systemic diseases like diabetes. In pediatric peritoneal dialysis special attention must be paid to the psychosocial advantage of intraperitoneal drug administration, especially when intraperitoneal administration can avoid the use of the subcutaneous injections. Subcutaneous administration of drugs is painful and distressing for both the child and his or her caregivers. Studies on the compliance with the subcutaneous administration of growth hormone reveal that noncompliance varies between 50 and 91% (177–179). In adult patients a noncompliance

with subcutaneous administration of erythropoietin was reported for 35% (180) and 55% of the patients (181). Independent predictors of noncompliance are reported to be younger age, completion of postsecondary education and missing dialysis exchanges (180).

8.1 Erythropoietin

The pharmacological development of human recombinant erythropoietin has been a major development in the treatment of renal anemia. This hormone is normally produced by a fibroblast-like cell population in the cortical interstitium of the kidney and induces proliferation and differentiation of erythroid progenitor cells in the bone marrow, resulting in an increase in circulating red blood cells. Anemia in patients with chronic renal failure is an important clinical problem, affecting over 90% of patients. The anemia is primarily caused by a decreased production of erythropoietin by the diseased kidney (182) but is also caused by a decreased red blood cell survival (183) and a decreased response to erythropoietin (184).

Since the introduction of recombinant human erythropoietin numerous studies have demonstrated the effectiveness of erythropoietin in preventing and treating renal anemia in patients with chronic renal failure, which subsequently decreased the need of blood transfusions. Both American (185) and European (186) best practice guidelines are available for the management of anemia in chronic kidney disease, however they pay hardly any attention to pediatric patients.

In pediatric dialysis most experiences have been obtained with subcutaneous administration of recombinant human erythropoietin (187,188). However despite some initial discouraging but still frequently cited reports (189,190) recombinant human erythropoietin can be very well administered by the intraperitoneal route. Good absorption of erythropoietin from the peritoneal cavity was observed in an animal model, if erythropoietin was administered in a small amount of dialysis fluid (191) and this was confirmed for humans (192). The first positive results using intraperitoneal erythropoietin were described in adult patients (193). Subsequently it was demonstrated in pediatric peritoneal dialysis patients that, if administered in a small amount of dialysis fluid (50 mL), the bioavailability of erythropoietin is similar to that after subcutaneous administration (194). A study performed in a small group of children showed that the dosage needed for intraperitoneal administration is similar to the dosage needed with subcutaneous administration if the hormone is administered in 50 mL of dialysis fluid (195). In chapter 3 we will confirm these results in a larger patient group.

The major concern using the intraperitoneal administration route is dialysis adequacy, since the hormone has to be administered in a very small amount of dialysis fluid, not allowing a regular dwell at the same time. However if adequacy targets can be reached without the need of daytime dwells, as in most children treated by NIPD, the intraperitoneal administration should be the preferred mode of administration. Guidelines concerning the management of anemia in pediatric patients have been published (196).

Recently Casadevall et al reported the development of pure red-cell aplasia during treatment with recombinant human erythropoietin in adult patients, which worsened the initial anemia and made all patients dependent on blood transfusions (197). In all patients neutralizing antibodies against erythropoietin were detected. Currently a worldwide discussion is ongoing concerning the management of this major side effect of erythropoietin treatment (198–202).

8.2 Antibiotics

Peritonitis remains one of the major complications of peritoneal dialysis both in adults (75) and in children (203,204). Treatment with intraperitoneal antibiotics is generally preferred as this route may be more effective than the intravenous or oral route and also results in the highest local antibiotic levels (205). Especially in children, who will be dependent on their peritoneum for prolonged periods of time, it is important to provide the highest efficacy of treatment in combination with a low potential of side effects like ototoxicity and nephrotoxicity.

There are many published antibiotic regimens for the treatment of peritonitis in peritoneal dialysis. In an effort to standardize the treatment of peritonitis in peritoneal dialysis patients, the Advisory Committee on Peritoneal Management of the International Society for Peritoneal Dialysis established guidelines (206). These guidelines recommended the intraperitoneal use of a combination of a first-generation cephalosporin and an aminoglycoside. The guidelines have been periodically updated as new information became available (207–209). The most recent edition of the guidelines advocates the use of a combination of a first-generation cephalosporin (cephalotin or cephazolin) and a third-generation cephalosporin (ceftazidime) (209). These recommendations are meant for adult patients in the first place but have also been followed for pediatric patients. However recently separate pediatric guidelines were published (210). They recommend the use of a combination of a glycopeptide and ceftazidime, a combination that also has been advocated by the guidelines for adults published in 1993 (207), but which was abandoned because of the increasing concerns about the risk of the occurrence of multi-resistant microorganisms due to the widespread use of vancomycin (208). As the administration of glycopeptides in children carries the same risks as in adults, their use should be restricted to selected patients. In chapter 4 we present our experiences with the use of a combination of a first- and a third-generation cephalosporin in unselected patients.

Aim and outline of this thesis

Peritoneal dialysis takes an important place as a treatment modality for children with chronic renal failure. This dialysis modality has important advantages compared to hemodialysis: it allows children of all ages to receive dialysis at home with the subsequent experience of a more normal childhood, and avoids repeated needle punctures other than those needed for drug administration. On the contrary this treatment modality places a significant burden both on the child and his or her caregivers. Peritoneal dialysis also implies that

attention has to be paid to the functionality of the peritoneal membrane, because most children will depend on it for a major part of their life. Therefore the aim of the studies presented in this thesis, was to evaluate several issues that might be of use in decreasing the psychosocial and physical burden. An attempt was made to study the fluid kinetics of a more biocompatible, glucose polymer based dialysis solution. Furthermore attention was paid to diminish the need of subcutaneous drug administration and to avoid the toxic effects caused by antibiotic treatment of peritonitis. Gastric emptying was studied to obtain more insight in gastro-enterological complications of peritoneal dialysis and the non-invasive treatment of peritoneal dialysis catheter obstruction and leakage of dialysis fluid was evaluated.

An overview of the current knowledge on peritoneal dialysis in children is described in the **General Introduction**. The current knowledge on peritoneal solute and fluid transport is summarized and several factors changing peritoneal permeability are discussed. Experiences with intraperitoneal administration of drugs are described briefly and attention is paid to the glucose polymer based dialysis solution icodextrin.

In **Part II** peritoneal fluid kinetics with the use of icodextrin and the influence of different osmotic agents on intraperitoneal pressure are presented.
Chapter 1 describes the assessment of peritoneal transport characteristics using the glucose polymer based dialysis solution icodextrin. A comparison is made with fluid kinetics using 3.86% glucose solution and results are compared with results obtained in adults.
In **Chapter 2** reference values of the intraperitoneal pressure in children are obtained and the Peritoneal Equilibration Test was applied to evaluate the influence of different dialysis fluids on the intraperitoneal pressure.

In **Part III** experiences with the intraperitoneal administration of different drugs are presented.
Chapter 3 investigates the maintenance dosage needed when erythropoietin is administered intraperitoneally instead of subcutaneously.
In **Chapter 4** the effectiveness of the use of a combination of a first- and a third-generation cephalosporin for the initial treatment of peritonitis is studied.

Finally **Part IV** concerns some important complications of peritoneal dialysis.
In **Chapter 5** an attempt is done to gain more insight into the gastroenterological complications of children treated with peritoneal dialysis.
Chapter 6 describes experiences with the use of urokinase in treating peritoneal dialysis catheter obstruction.
Chapter 7 presents the results of the use of fibrin glue in catheter leakage in acute peritoneal dialysis.

Finally **Part V** contains a general discussion and **Part VI** contains a summary, a summary in Dutch and a summary for readers unknown to the subject in Dutch.

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Part II

Peritoneal transport

1

Peritoneal transport characteristics with glucose polymer-based dialysis fluid in children

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Abstract

Scarce data are available on the use of glucose polymer based dialysate in children. The effects of glucose polymer based dialysate on peritoneal fluid kinetics and solute transport were studied in pediatric patients on chronic peritoneal dialysis and a comparison was made with previously published results in adult patients. In 9 children 2 peritoneal equilibration tests were performed using 3.86% glucose and 7.5% icodextrin as a test solution. Dextran 70 was added as a volume marker to calculate fluid kinetics. Serum and dialysate samples were taken for determination of urea, creatinine, and sodium. After calculation of the initial transcapillary ultrafiltration rate it was possible to calculate the contribution of aquaporin mediated water transport to ultrafiltration for icodextrin and 3.86% glucose and the part of LpS (the product of the peritoneal surface area and the hydraulic permeability) caused by aquaporins. In children the transport parameters were similar for the two solutions, except for transcapillary ultrafiltration (TCUF) which was lower for icodextrin (0.9 ml/min/1.73 m^2) as compared with 3.86% glucose (4 ml/min/1.73 m^2). Transport parameters were similar in children and adults for glucose, but with icodextrin TCUF and marker clearance were significantly lower in children. Aquaporin mediated water flow was 83 versus 50% with glucose (child versus adult) ($P<0.01$) and 18 versus 7% with icodextrin ($P<0.01$). Data indicate that transport parameters in children using icodextrin are similar to glucose except for TCUF. Differences are explained by the absence of crystalloid osmosis and the fact that TCUF was determined after a 4-hour dwell. Comparison of transport parameters and peritoneal membrane characteristics reveal that there seem to be differences in the amount and functionality of aquaporins between pediatric and adult patients. However there are no differences in clinical efficacy of this transport pathway since the absolute flow through the aquaporins is identical in both groups using 3.86% glucose.

Keywords:

Icodextrin, 3.86% glucose, fluid kinetics, solute transport, aquaporin, peritoneal dialysis.

Introduction

Icodextrin contains glucose polymers as osmotic agent instead of glucose in the conventional peritoneal dialysis solutions. The effectiveness of icodextrin as a colloid osmotic agent has been very well established in adult patients (1-4). The solution is especially indicated in situations where a high exposure to glucose should be avoided such as in patients with exchanges with a long dwell time and in patients with ultrafiltration failure (5).

Until now very little has been published about the use of glucose polymer based dialysate in children. It was demonstrated that 7.5% icodextrin is capable of inducing sustained net ultrafiltration during long term dwell in children and that the metabolism of icodextrin is similar compared to adults (6). The aim of the present study was to compare a 7.5% icodextrin based dialysis solution with a 3.86% glucose solution with regard to peritoneal fluid kinetics and solute transport in a pediatric peritoneal dialysis population. Additionally the results obtained in children were compared with results obtained in adult patients, which were previously published (5). A brief summary of the study in adult patients will be given in the Methods section.

Methods

Pediatric study

The patient group consisted of 4 girls and 5 boys, with a median age of 4.9 years (range 1.6 – 10.9). The mean duration of nightly intermittent peritoneal dialysis treatment was 26.2 months (range 5.6 – 122.3). In each patient 2 Peritoneal Equilibration Tests were performed, using a different test solution for each Peritoneal Equilibration Test. The solutions used were a 7.5% icodextrin solution (Extraneal®, Baxter B.V. Utrecht, The Netherlands) and a 3.86% glucose solution (Dianeal®, Baxter B.V. Utrecht, The Netherlands). All Peritoneal Equilibration Tests were performed as previously described by Reddingius et al (7). An intraperitoneal volume of 1200 mL/m^2 body surface area (BSA) was used in all tests. Dextran 70 (Macrodex NPBI, Emmercompascuum, The Netherlands) was added to the dialysate as a volume marker to calculate fluid kinetics. A serum sample was taken at the start of the study. Dialysis fluid was sampled before inflow, after 5, 30, 60, 120, 180 minutes and at the end of the test at 240 minutes. These samples were used for measurement of dextran, glucose, creatinine, urea and sodium. All Peritoneal Equilibration Tests were performed at least two months after any peritonitis episode. None of the patients had ultrafiltration failure.

Calculations

For the calculations the principles of Nolph et al. were applied (8), adapted by Krediet et al. (9). Transport parameters were calculated according to previously described formulas (7). In brief transcapillary ultrafiltration (TCUF) was calculated from the dilution of the volume marker, by subtracting the initial theoretical intraperitoneal volume (IPV) from the theoretical IPV. The theoretical IPV is the IPV in the absence of marker clearance and

sampling, in which marker clearance equals the disappearance of fluid from the peritoneal cavity. The initial TCUF for the glucose solution and the icodextrin solution, meaning the TCUF during the first minute of a dwell ($TCUF_{0\text{-}1min}$) were calculated according to the Lineweaver-Burk plot for the glucose-based solution and by linear regression for the icodextrin-based one (9). The transcapillary ultrafiltration rate (TCUFR) was obtained by dividing TCUF by the dwell time.

The change in IPV (Δ-IPV) was obtained by calculating the dilution of the volume marker after correction for incomplete recovery. The net ultrafiltration rate was obtained by dividing Δ-IPV by the dwell time. Marker clearance was defined as the difference between the amount of dextran instilled and the total amount recovered, divided by the product of dwell time and the mean dextran concentration. Marker clearance rate was calculated by dividing marker clearance by the dwell time. It was assumed that marker clearance is a linear process. The mass transfer area coefficient (MTAC) is the maximal theoretical diffusive clearance of a solute at time 0, before transport has actually started. The MTAC of urea and creatinine were calculated according to the Waniewski model (10), in which a correction for plasma water concentrations was used (5).

The dialysate / plasma ratio of sodium was used to analyze the sieving of sodium during the first hour of the dwell for the 3.86% glucose and the 7.5% icodextrin Peritoneal Equilibration Test.

Glucose induces ultrafiltration by increasing the crystalloid osmotic pressure in the peritoneal cavity, which induces fluid transport across the small interendothelial pores and also through the ultrasmall transcellular pores (aquaporins). The effect of glucose on the large pores can be neglected because of their very small number and large pore size. The colloid osmotic pressure induced by icodextrin almost exclusively exerts its effect across the small pores. This implies that the ultrafiltration coefficient (UFC) of the transcellular pores (UFC_{aqp}) can be calculated from the difference between the total UFC (UFC_{tot}) of the peritoneum, as calculated with 3.86% glucose, and the UFC of the small pores (UFC_{sp}), as calculated with icodextrin:

$$UFC_{aqp} = UFC_{tot} - UFC_{sp}$$

The UFC was calculated as previously described by Ho-Dac-Pannekeet et al. (5). A description of the calculations is given in appendix A.

The UFC is the product of the hydraulic permeability of the peritoneum (Lp) and the surface area (S). After calculation of the contribution of the transcellular pores to UFCtot, it is possible to calculate the fractional transcellular UFC, meaning the part of LpS that is caused by AQPs. Subsequently it is possible to calculate the fractional osmotic force exerted across the AQPs. Calculations of the fractional transcellular UFC and the fractional osmotic force across AQPs were performed using the formulas described by Krediet et al. (11). A description of the calculations is given in appendix B. Calculations of the fractional transcellular UFC and the fractional osmotic force across aquaporins were also performed for the adult patient group.

Statistical analyses

Results are given as mean and median values, SD and ranges. For comparison of the results of the two solutions within the pediatric group, a paired Student-t test was performed. Differences between children and adults were tested with the Mann-Whitney nonparametric rank test. Correlations were tested using the Spearman rank correlation analysis.

Study in adult patients

Ho-Dac-Pannekeet et al. previously published a study about peritoneal transport characteristics with icodextrin performed in adults (5). Results obtained in this study were used (with kind permission of Ho-Dac-Panekeet et al.) to make a comparison with the results of our study, which was performed in children. The patient group of Ho-Dac-Pannekeet et al. consisted of 10 stable patients, with a median age of 48 years (range 23-64). The mean duration of CAPD treatment was 28 months (range 3-92). In each patient 3 peritoneal equilibration tests were performed, using a different test solution for each peritoneal equilibration test. The three test solutions consisted of 1.36% glucose, 3.86% glucose and 7.5% icodextrin. The peritoneal equilibration test was standardized in the same way as in the pediatric study. Dialysate samples were taken at 10, 20, 30, 60, 120, 180 and 240 minutes. Blood samples were drawn at the beginning and at the end of the period. In the glucose dwells dextran 70 was added as a volume marker, whereas in the icodextrin dwell dextrin itself was used for that purpose. Calculations of transport parameters were made based on the same principles as those used in the pediatric study. Calculations of the fractional transcellular UFC and the fractional osmotic force across aquaporins were not part of the adult study.

Results

The medians and ranges of fluid and solute transport parameters of children and adults obtained with 3.86% glucose and 7.5% icodextrin are given in Table 1. All data are expressed per 1.73 m^2 body surface area.

Fluid transport

The TCUFR with icodextrin was significantly lower compared to the TCUFR obtained with glucose 3.86% in our study group ($P < 0.001$). The marker clearance rate, and net ultrafiltration rate were similar for the two solutions. Fluid profiles for 3.86% glucose and 7.5% icodextrin are given in Figure 1.

Transport parameters for fluid transport using 3.86% glucose were similar for children and adults. For 7.5% icodextrin the TCUFR in children was significantly lower than in adults ($p < 0.01$). Also the marker clearance rate was significantly lower ($p<0.02$). The net ultrafiltration rate however was not significantly different from adult patients ($p = 0.27$). Consequently the Δ-IPV was also similar for children and adults ($p = 0.36$).

Solute transport

The transport of the low molecular weight solutes creatinine and urea in children was

	3.86% Glucose		7.5% Icodextrin	
	Median	**range**	**Median**	**range**
MTACurea ml/min/1.73 m²				
Child	15.4	11.9-21.2	24.9	17.6-24.9
Adult	19.1	12-27	14.1	6-26
MTACcreat ml/min/1.73 m²				
Child	9.3	6.4-10.9	8.6	5-13.8
Adult	11.7	6-21	14.3	7-24
TCUFR ml/min/1.73 m²				
Child	4.0	1.6-5.4	0.9	0.5-1.9[a ,b]
Adult	4.5	0.5-6.4	2.3	1.4-4.8
MCR ml/min/1.73 m²				
Child	1.3	0.1-10.8	0.4	0-2.0[c]
Adult	1.0	0.2-4.4	1.1	0-6.8
NUFR ml/min/1.73 m²				
Child	3.0	-9.3-4.2	0.2	-1.6-1.8
Adult	3.2	-1.5-5.1	1.1	-2-2.3
Δ-IPV ml/1.73 m²				
Child	715.8	-224.2-1006.6	52.1	-394.6-443.3
Adult	724	-274-1127	227	-437-527
Time on PD months				
Child	12	5.6-122.3		
Adult	28	3-92		
D/P creatinine				
Child	0.57	0.52-0.83	0.61	0.41-0.63

Table 1. Comparison of fluid and solute transport parameters in children and adults during a 4-hour dwell with 3.86% glucose and 7.5% icodextrin.
Adult data are obtained from a previously published study (5). Mass transfer area coefficient of urea (MTACurea), mass transfer area coefficient of creatinine (MTACcreat), transcapillary ultrafiltration rate (TCUFR), marker clearance rate (MCR), net ultrafiltration rate (NUFR), Δ-intraperitoneal volume (Δ-IPV) and D/P creatinine (dialysate/plasma ratio creatinine). Statistical analysis was performed with Mann-Whitney nonparametric test.
[a] p<0.01 3.86% glucose versus icodextrin
[b] p<0.01 children versus adults
[c] p=0.02 children versus adults

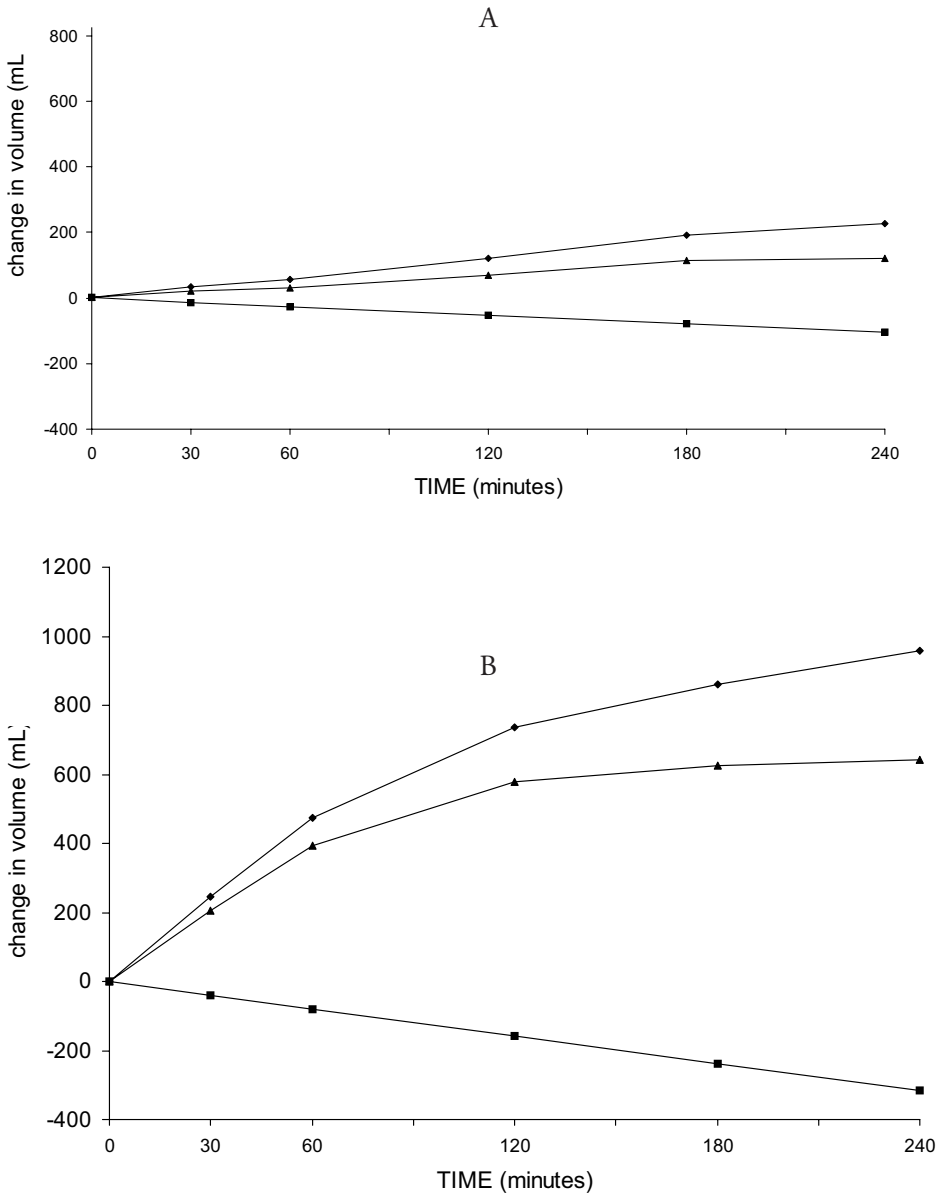

Figure 1. Changes of intraperitoneal volume (ml/1.73 m²) in time. Transcapillary ultrafiltration (♦), marker clearance (■) and net ultrafiltration (▲) during a 4-hour dwell in children using 7.5% icodextrin (A) and 3.86% glucose (B). TCUF after 4 hours was significantly lower during the icodextrin Peritoneal Equilibration Test ($p<0.01$). Ultrafiltration and marker clearance after 4 hours were similar for 3.86% glucose and icodextrin.

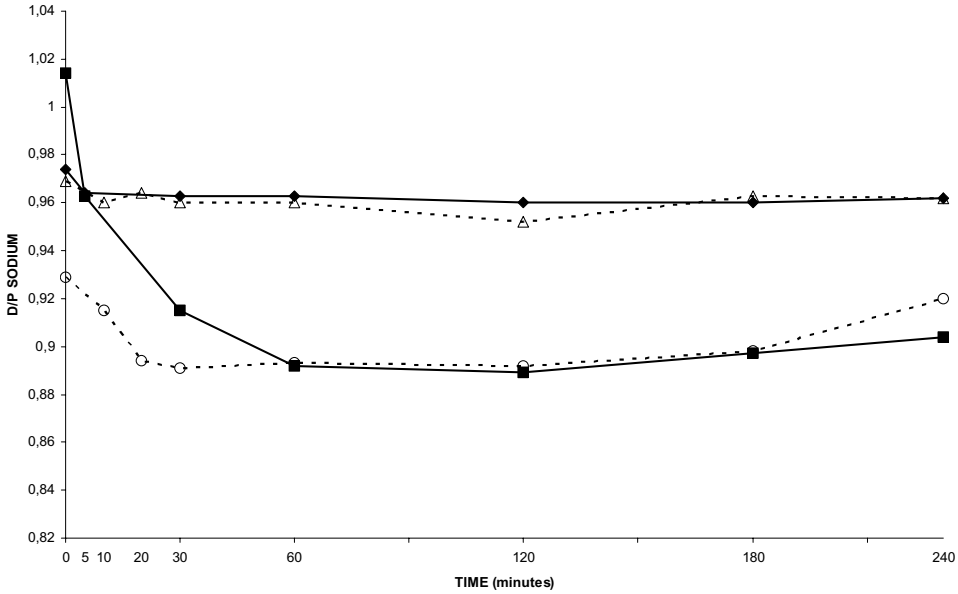

Figure 2: Dialysate / plasma ratios of sodium during 4-hour dwells with 3.86% glucose (■) and 7.5% icodextrin (♦) in children (solid lines) and for 3.86% glucose (○) and 7.5% icodextrin (Δ) in adults (dotted lines). The dialysate sodium concentration decreases with 3.86% glucose because aquaporin mediated water transport exceeds the effect of sodium diffusion. Icodextrin induced no changes in dialysate / plasma sodium.

similar for both solutions. A correlation was found between net ultrafiltration rate and $MTAC_{creat}$ (r=0.69, p<0.04) in the icodextrin dwell, which was not found in the glucose dwell. No relation was found between $MTAC_{creat}$ and age or time on PD.

No significant differences were found between children and adults. A marked dip in dialysate / plasma ratio of sodium was found in the initial phase of the 3.86% glucose dwell, which was absent in the dwell with the icodextrin solution (Figure 2).

Contribution of the aquaporins to the peritoneal ultrafiltration coefficient

The mean UFC_{tot} calculated with 3.86% glucose solutions was 0.12 ± 0.002 ml/min/mm Hg. The AQPs contributed 83.4 ± 6.4% to this value. In the adult patient group the AQPs contributed 50.5 ± 12% to a mean total UFC of 0.18 ± 0.04 ml/min/mm Hg (P < 0.01). The mean UFC_{aqp} in children was 0.10 ± 0.02 ml/min/mm Hg and 0.12 ± 0.10 ml/min/mm Hg in adults (P = 0.64)

Both in children and adults there was no significant correlation between the UFC_{aqp} and duration of PD treatment (children r = 0.58, NS; adults r = -0.56, NS) , or age (children r = -0.12, NS); adults r = 0.19, NS).

The mean fractional transcellular UFC calculated using 3.86% glucose was 0.15 ± 0.06 mL/min/mm Hg in children and 0.05 ± 0.04 mL/min/mm Hg in adults ($P < 0.001$) which implies that the AQPs are responsible for respectively 15% and 5% of the L_pS. The fractional transcellular UFC in children showed a significant negative correlation with the duration of PD treatment ($r = -0.67$, $P < 0.05$) but showed no correlation with age ($r = 0.13$, NS). In adults there was no significant correlation with duration of treatment or age. The mean fractional osmotic force exerted across AQPs using 7.5% icodextrin was 0.18 ± 0.07 mL/min/mm Hg in children and 0.07 ± 0.06 mL/min/mm Hg in adults ($P < 0.001$), implying that respectively 18% and 7% of the water flow occurs through the AQPs during a dwell with icodextrin.

Discussion

During the last ten to fifteen years there is a growing recognition of the need for the development of dialysis solutions, which are more biocompatible than the standard commercially available glucose based solutions. Icodextrin is mainly characterized by the absence of glucose. Instead long-chain glucose polymers are present which are responsible for ultrafiltration. Ultrafiltration occurs according to the principle of colloid osmosis. The absorption of glucose polymers is limited which gives rise to a prolonged persistence of the colloid osmotic gradient. The use of icodextrin has been extensively studied in adult patients. It has been shown that the daily use of icodextrin is safe, generally well tolerated and it can replace the daily overnight use of hyperosmotic glucose solutions (2,3). Posthuma et al. demonstrated that icodextrin could also be very well used in an automated peritoneal dialysis regimen to enhance ultrafiltration during the long daytime dwell (12). The use of icodextrin is associated with a significant increase in serum concentrations of icodextrin metabolites, which however has not been associated with clinical adverse events (3,12).

Until know very little is published about the use of glucose polymer based dialysate in children. In a previous study it was demonstrated that the addition of a daytime icodextrin dwell to a Nightly Intermittent Peritoneal Dialysis regimen in children results in an increase of both ultrafiltration and adequacy of dialysis and that the metabolism of icodextrin occurs at a similar rate compared to that in adults (6). However there are no data available with respect to the effect of icodextrin on the peritoneal fluid kinetics and solute transport. The present study describes the behavior of icodextrin in the peritoneal equilibration test in children and compares the results with previously published data obtained in adults (5).

The values of fluid transport parameters with 3.86% glucose found in the present study, were within the ranges of those found in a previous study performed in pediatric patients (13). The transcapillary ultrafiltration with icodextrin was different from that obtained with 3.86% glucose. This can be explained by the fact that ultrafiltration was measured after a 4-hour dwell time; 3.86% glucose gives rise to a rapid ultrafiltration in the beginning of the dwell which diminishes in time because of dissipation of the osmotic gradient, whereas icodextrin gives rise to a slow but sustained ultrafiltration during a prolonged period because of the limited absorption of the glucose polymers (14).

Icodextrin in children

Fluid kinetics for 3.86% glucose are similar in children and adults. This is in accordance with a previous study that showed that fluid kinetics in different age groups are comparable if corrected for body surface area (13,15). Based on these observations it is expected that fluid kinetics for icodextrin are also similar between the different patient groups. Results previously published by the Boer et al. already showed that net ultrafiltration obtained with icodextrin is similar for children and adults after a long term dwell (6). However our results are not fully in accordance with the expectations. Net ultrafiltration is similar for both groups, but transcapillary ultrafiltration and marker clearance are significantly lower in children. Rippe et al. demonstrated an advantage of using icodextrin in patients with an increased effective vascular area, because icodextrin will produce an increased ultrafiltration rate when the vascular surface area is increased (16). The difference in transport parameters using icodextrin between adults and children may thus be explained by a difference in effective vascular surface area. Although a statistical difference in treatment period is not present, there seems to be an overrepresentation of long-term dialysis in the adult patient group. Long-term dialysis is associated with neoangiogenesis in the peritoneum (17-19) which can explain an increase in the effective peritoneal surface area. However there was no significant difference in $MTAC_{creat}$, which indicates that there is no difference in the effective peritoneal surface area. Due to the small sample of patients we also have to realize that statistical comparison is easily bothered by chance observations. Based on these results it is therefore not possible to give an explanation for the differences seen in marker clearance and transcapillary ultrafiltration. As the net ultrafiltration is similar for children and adults it is most likely that in clinical practice there are no differences to be expected.

Osmotic effect of icodextrin on the peritoneal membrane

Based on the three-pore model of peritoneal transport suggested by Rippe et al (20,21) the aquaporins play a minor role in transcapillary ultrafiltration when using icodextrin but a major role in transcapillary ultrafiltration when using 3.86% glucose. This is demonstrated by the significant difference in contribution of aquaporins using 3.86% glucose or icodextrin in both children and adults. This difference can be visualized by analyzing the difference in sodium sieving during the first hour of a dwell. As the water flow through the aquaporins will exceed the flow of water and small solutes through the small pores using 3.86% glucose, it will cause a fall in the sodium dialysate concentration. Using icodextrin there will be no fall in sodium dialysate concentration. In the present study this different role of the aquaporins is very well visualized. Using 3.86% glucose the dialysate / plasma ratio of sodium decreased, whereas using icodextrin the dialysate / plasma ratio did not change. The sodium dialysate / plasma curves are similar for children and adults, suggesting a similar role for aquaporins both in children and adults. The theory that transport through the small pores is of great importance for the action of 7.5% icodextrin is supported by the fact that both in children and adults a relation was found between the mass transfer area coefficient of creatinine and transcapillary ultrafiltration, while this relation was not found using 3.86% glucose.

However our calculated data show a significant difference in the water flow through the aquaporins in both glucose and glucose polymer induced ultrafiltration is present between children and adults. This difference diminished as we calculated the absolute amount of the contribution of the aquaporin-mediated waterflow to the total ultrafiltration coefficient (see below).

Functional characterization of the peritoneal membrane

The UFC is the product of the peritoneal surface area (S) and its hydraulic permeability (L_p). In children 15% of the L_pS is determined by aquaporins versus 5% in adults. This implies that the children in our study group have a 3 times higher amount of functional aquaporins as compared to the individuals in the adult study group. Lai et al (22) demonstrated that transcription and biosynthesis of AQP-1 in human peritoneal mesothelial cells is significantly increased upon exposure to glucose *in vitro*. This upregulation of AQP-1 upon exposure to glucose is time- and dose-dependent. They also demonstrated an absence of AQP-1 in peritoneal lining denuded of mesothelial cells and speculated that long-term PD might lead to decreased expression of AQP-1 on the peritoneal lining because of denudation of mesothelium. The negative correlation between the fractional trancellular UFC and treatment period in children indeed suggests a decreased expression of AQP in long-term PD. The absence of a relation between fractional transcellular UFC and age implies that the differences observed in AQP function are not related to age groups, but are determined by other factors as duration of treatment and glucose exposure. It is also important to realize that the age range of the pediatric patients was small, as was the number of our observations. The current methodology makes it impossible to compare the (cumulative) glucose exposure between both study groups. A recent study has shown that aquaporins can be inactivated while they remain on the cell surface (23). This implies that inactivation of aquaporins can be accomplished through means other than degradation of the water channels. It is not yet clear what mechanism is responsible for the inhibition of the aquaporins but maybe this might be an explanation for the differences found between children and adults. It also should be considered that the differences in the amount of functional aquaporins are the result of a lower small pore area in the children. As the children are smaller they do have lower actual small pore areas. However by adjusting both the dwell volume and the transport parameters to the body surface area such differences between adults and children are no longer expected. This is confirmed by the fact that the MTACs for small solutes are the same in children and adults, which means that the functional size of the small pore area will not be essentially different.

Next to the observation of differences in the amount of functional AQPs, the AQP-system seems also more efficient in the pediatric study group, because 83% of glucose induced ultrafiltration takes place through these aquaporins compared to 50% in adult patients. The effectiveness of the system can be explained by the fact that L_pS is a physical quantity that is defined based on hydrostatical pressure (expressed as ml/min/mm Hg). The resistance caused by the ultrasmall aquaporins is much larger than the resistance caused by the small pores. The reason why such a great part of the ultrafiltration occurs through the

aquaporins is because PD is based on a crystalloid osmotic pressure instead of a hydrostatic pressure.

Further calculations show that the total amount of water, transported through the aquaporins during a glucose dwell (UFC_{aqp}) is the same for children and adults. This implicates – although it seems that there are differences in the aquaporins between both study groups – that the effect of the 3.86% glucose solution on the aquporins is exactly the same.

It can be concluded that fluid and solute parameters are similar for glucose polymer based dialysate and 3.86% glucose in children, except for the transcapillary ultrafiltration. This can be explained by the absence of crystalloid osmosis and the fact that TCUF was measured after a 4-hour dwell.

Comparison of transport parameters and peritoneal membrane characteristics reveal that there seem to be differences between the peritoneal transport pathways in children and adults, but these differences do not interfere with the clinical efficacy of the aquaporins since the absolute water flow through the aquaporins is identical in both groups using 3.86% glucose. Further studies are needed to explore the differences between children and adults in the amount and the functionality of the aquaporins and the small pores.

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Appendix A

The ultrafiltration coefficient (UFC) can be calculated from the following equation:

$$TCUFR = UFC\ [\Delta P - \sigma\Delta\Pi + \sigma\Delta O] \qquad \text{(Eq. 1)}$$

in which $TCUFR_{0\text{-}1\ min}$ is the maximal transcapillary ultrafiltration rate obtained during the firts minute of an exchange, ΔP is the hydrostatic pressure gradient, $\Delta\Pi$ is the colloid osmotic pressure gradient, and ΔO is the crystalloid osmotic pressure gradient. σ is the reflection coefficient that can range from 1.0 (ideal semipermeable membrane) to 0 (no osmotic effect). It was assumed that ΔP, during PET, has a constant value of 9 mm Hg, as the capillary pressure is about 17 mmHg (24) and the intraperitoneal pressure 8 mm Hg while resting (25). According to Van 't Hoffs law every mOsm/liter exerts an osmotic pressure of 19.3 mm Hg in the case of an ideal semipermeable membrane. This implies that the osmotic pressure generated by an osmotic gradient is given by : [osmolality $\cdot\sigma\cdot$ 19.3]. The reflection coefficient of albumin is generally considered to approach 1.0. The reflection coefficient of icodextrin was calculated using the relation between reflection coefficients of low molecular weight solutes (urea, urate, glucose, creatinine), and albumin, and their molecular weights. The molecular weight of icodextrin (16,800 Da) resulted in a value of 0.767 for the reflection coefficient. The capillary colloid osmotic pressure (Π_c) was assumed to be determined by the serum albumin concentration for 75% (26). To this value 0.04 was added because of the Gibbs-Donnan equilibrium (26).

$$\Pi_c = \left[\frac{SA \cdot 1000}{68{,}000}\frac{4}{3} + 0.4\right] \cdot 19.3 \qquad \text{(Eq. 2)}$$

$$= 0.38\ SA + 7.72\ mm\ Hg$$

In this equation SA represents serum albumin (g/liter), 68,000 is the molecular weight of albumin, and the factor 1000 converts osmoles to mosmoles. The osmotic pressure within the peritoneal cavity (Π_{pc}), exerted by icodextrin, equals:

$$\Pi_c = \left[\frac{DIC \cdot 1000}{16{,}800}\right] \cdot 0.767 \cdot 19.3 \qquad \text{(Eq. 3)}$$

$$= 0.88DIC$$

in which DIC is the dialysate icodextrin concentration in g/liter, 16,800 is the molecular weight of icodextrin, and 0.767 is the reflection coefficient.

Therefore the transcapillary ultrafiltration rate through the small pores ($TCUFR_{sp}$) during the initial phase of the exchange, before absorption of solutes has taken place, equals:

$$TCUFR_{sp} = UFC_{sp}[\Delta P - (\Pi_c - \Pi_{pc})] \qquad \text{(Eq. 4)}$$

$$= UFC_{sp}[9 - 0.38SA - 7.72 + 0.88DIC]$$

$$= UFC_{sp}[1.28 + 0.88DIC - 0.38SA]$$

The transcapillary ultrafiltration during the first minute of the dwell was considered to represent the initial transcapillary ultrafiltration rate.

It implies that the UFC of icodextrin (ID) can be written as:

$$UFC_{sp} = \frac{TCUFR_{0\text{-}1min}\ (ID)}{0.88DIC - 0.38SA + 1.28}\ (ml/min/mm\ Hg)\ (Eq.\ 5)$$

For 3.86% glucose a similar equation can be given:

$$TCUFR_{0\text{-}1min} = UFC_{tot}[\Delta P - \Pi_c + \sigma\Delta O] \quad (Eq.\ 6)$$

ΔP was kept constant at 9 mm Hg and Π_c was calculated according to [Eq. 2]. ΔO is the difference between the osmolality of the dialysis fluid (486 mOsm/liter) and the plasma osmolality of the patient (Osm). As σ glucose averages 0.03 (27), $\sigma\Delta O = 0.03 \cdot (486 - Osm) \cdot 19.3$ mm Hg. Substitution of these numbers in [Eq 6] yields:

$$TCUFR_{0\text{-}1min} = UFC_{tot}[9 - 0.38SA - 7.72 + 0.03(486 - Osm) \cdot 19.3] \quad (Eq.7)$$

Rearranging this equation yields:

$$UFC_{tot} = \frac{TCUFR_{0\text{-}1min}\ (3.86\%)}{283 - 0.38SA - 0.58Osm}\ (ml/min/mm\ Hg)\ (Eq.\ 8)$$

Subtraction of equation (5) from equation (8) gives the UFC of the aquaporins:

$$UFC_{aqp} = \frac{TCUFR_{0\text{-}1min}\ (3.86\%)}{283 - 0.38SA - 0.58Osm} - \frac{TCUFR_{0\text{-}1min}\ (ID)}{0.88DIC - 0.38SA + 1.28} \quad (Eq.\ 9)$$

Appendix B

The ultrafiltration coefficient is the product of the hydraulic permeability of the peritoneum (L_p) and the surface area (S). It can be calculated from the initial transcapillary ultrafiltration rate and the overall peritoneal pressure gradient according to Starling's equation (see Appendix A):

$$TCUFR_{0\text{-}1min} = L_pS[\Delta P - \sigma\Delta\Pi + \sigma\Delta O] \quad \text{(Eq. 10)}$$

There are apparent differences for L_pS values calculated using either icodextrin or glucose, while L_pS is a membrane constant that is constant by definition. The most probable explanation is the heteroporosity of the peritoneum. The presence of aquaporins is especially important in this respect because they represent only a small proportion of the surface area, but contribute largely to water flow induced by crystalloid osmosis. Despite the small contribution by aquaporins to total peritoneal L_pS, a very large proportion of the osmotic force is exerted across this pathway. This is because the osmotic force is composed of the fractional UFC values (across small pores and aquaporins), each multiplied by the solute reflection coefficient across each pore system.

For glucose the following calculation can be made, assuming a reflection coefficient of 1.0 across the aquaporins and 0.03 across the small pores.

The partial osmotic forces are as follows:

$$\text{Aquaporins:} \quad X \cdot L_pS \cdot 1.0 \quad \text{(Eq. 11)}$$

$$\text{Small pores :} (1\text{-}X) \cdot L_pS \cdot 0.03 = L_pS[0.03 - 0.03X] \quad \text{(Eq. 12)}$$

in which X is the the part of L_pS caused by aquaporins.

The fractional osmotic force across aquaporins now becomes:

$$\frac{X}{0.03 + 0.97X} = UFC_{aqp} \quad \text{(Eq. 13)}$$

in which UFC_{aqp} is the contribution of aquaporins to UFC_{tot} (see Appendix A, Eq. 9).

A similar calculation can be made for icodextrin, assuming a reflection coefficient of 1.0 across aquaporins and 0.767 across the small pores. The partial osmotic forces are as follows:

$$\text{aquaporins:} \quad Y \cdot L_pS \cdot 1.0 \quad \text{(Eq. 14)}$$

$$\text{small pores :} \quad (1\text{-}Y) \cdot L_pS \cdot 0.767 = L_pS[0.767 - 0.767Y] \quad \text{(Eq. 15)}$$

in which Y is the fractional osmotic force across aquaporins as calculated according to equation 13.

The fractional osmotic force across aquaporins now becomes:

$$\frac{Y}{0.767 + 0.233Y} = UFC_{aqp} \qquad \text{(Eq. 13)}$$

2

Evaluation of intraperitoneal pressure and the effect of different osmotic agents on the intraperitoneal pressure in children

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Abstract

Objective: To establish the intraperitoneal pressure (IPP) in a relatively large pediatric study group. To study the effect of a 3.86% glucose solution and a 7.5% icodextrin solution on IPP during a 4-hour dwell.

Design: IPP measurements with the patient in a supine position. The intraperitoneal volume (IPV) was 1200 ml/m² of a 1.36% glucose solution. The influence of dialysis solutions was obtained performing two 4-hour peritoneal equilibration tests (PETs) with 3.86% glucose and 7.5% icodextrin as a test solution respectively, using an IPV of 1200 ml/m^2 and Dextran 70 as a volume marker. The IPP was measured at 2 consecutive time points (t = 0 and 240 min). Transcapillary ultrafiltration (TCUF), net ultrafiltration (UF) and marker clearance (MC) were calculated.

Patients: IPP was established in 30 patients with a median age of 4.5 years (range 1.0-14.9). Influence of dialysis solutions on IPP was studied in 9 children with a median age of 4.2 years (range 1.7-10.9) and a median treatment period of 12 months (range 5.6-122.3).

Results: Mean IPP was 12.3 cmH_2O ± 6.4. A significant relation was found between the change in IPP and the TCUF and BSA during a PET with 3.86% glucose. No relations were seen during the PET with icodextrin.

Conclusions: IPP as established in a large pediatric study group is similar to previously published values of IPP in a small number of patients. Differences in fluid kinetics have different effects on the change in IPP during a 4-hour dwell period.

Keywords:

Peritoneal dialysis, children, intraperitonea pressure, icodextrin,3.86% glucoe soltiIntroduction

Introduction

The hydrostatic intraperitoneal pressure (IPP), measured in the supine position in patients on automated PD, has proven to be a valuable, objective tool to analyze the individual tolerance for intraperitoneal volume (1-5). Determination of an optimal intraperitoneal volume (IPV) enables optimization of solute clearance in combination with a dwell volume, which is well tolerated by the patient (3,5,6). As a consequence IPP is one of the parameters that should be measured if one wants to create an optimal individualized prescription of a dialysis regimen is desired. Besides the influence of the IPV on the IPP other parameters, such as age (7,8), body size (8,9) body mass index (8), time-induced adaptation (1) and degree of biocompatibility of the dialysis fluid used (10) also have impact on the IPP. Until now studies concerning the IPP in pediatric peritoneal dialysis (PD) were performed in small groups of only 6 to 8 children (2,3,6,7). Data on IPP in a larger study group are desirable. The influence of dialysis fluids containing different osmotic agents on the intraperitoneal pressure was also studied by comparing the intraperitoneal pressure and transport parameters using an icodextrin- and a 3.86% glucose-solution under similar test conditions in pediatric patients on chronic PD.

Methods

IPP measurement

The IPP was measured in a group of 30 children (19 boys, 11 girls) with a median age of 4.5 years (range 1.0-14.9) and a median duration of PD-treatment of 13 months (range 3.2-140.7). All children were in nightly intermittent peritoneal dialysis (NIPD). IPP measurements were performed at the occasion of a peritoneal equilibration test (PET), which is routinely performed every six months in children on chronic peritoneal dialysis. In each child one test was performed. Prior to instillation of the test solution for the PET, the peritoneal cavity was rinsed with 1200 ml/ m^2 body surface area (BSA) of a 1.36% glucose solution (Dianeal®, Baxter B.V. Utrecht, The Netherlands). The IPP was measured after completion of the inflow and just before drainage of the 1.36% glucose solution. The IPP was measured as described by Fischbach et al (4,5). The IPP was measured with the patient in a complete supine position. IPP was expressed in centimeters of water by measuring the height of the column of dialysate in the line of a disconnect system. The reference point was set at the center of the abdominal cavity, on the midaxillary line. Because we used single bag systems a trocar was introduced at the injection site of the bag, before the readings were made, to avoid counterpressure in the distal part of the measurement tubing. The level of the column of dialysis fluid was read after deep inspiration (IPPin) and after deep expiration (IPPex). Adding the IPPin and IPPex and dividing the addition sum by 2 determined the mean IPP.

Influence of different dialysis fluids on IPP

In a group of nine children (median age 5.5 years; range 1.8 – 12.5) we studied the influence of a 3.86% glucose solution and a 7.5% icodextrin solution on IPP and the change in IPP

	Mean ± SD	p-value[a]
IPP	12.0 ± 6.5	
Age	6.0 ± 3.9	NS
Duration PD	27.9 ± 37.2	NS
BSA	0.76 ± 0.25	NS
BMI	16.5 ± 1.4	NS

Table 1. IPP measurement in a group of 30 children
Results of IPP measurements and characteristics of the study group. In each patient one test was performed.
[a] = Spearman rank correlation analysis : relation between IPP and age, duration PD, BSA and BMI. There are no significant relations found between IPP and the other parameters
IPP = intraperitoneal pressure (cmH_2O), age (years), duration PD (months), BSA = body surface area (m^2), BMI = body mass index (kg/m^2)

in relation to fluid kinetics. In each child two PETs were performed as described previously (11); one PET was performed with a 3.86% glucose solution (Dianeal®, Baxter B.V. Utrecht, The Netherlands) and the other was performed with a 7.5% icodextrin solution (Extraneal®, Baxter B.V. Utrecht, The Netherlands). The 4-hour dwell was performed with an IPV of 1200 ml/ m^2 BSA and dextran 70 (Macrodex NPBI, Emmercompascuum, The Netherlands) was added to the test solution as a volume marker to calculate fluid kinetics. A serum sample was taken at the start of the study. Dialysis fluid was sampled at the start of the study and at 5, 30, 60, 120, 180 and 240 minutes after instillation of the test solution. The 2 PET's were performed with a median interval of 5.6 months (range 4.9-6.2 months) and all PET's were performed at least two months after any peritonitis episode. The IPP (cmH_2O) was measured at 2 distinct time points. The first IPP measurement (IPP1) was performed during the rinsing procedure before the 4-hour dwell, as described in the section IPP measurement. The second IPP measurement (IPP2) was performed directly after dialysate sampling at t= 240, just before drainage of the test solution.

The transcapillary ultrafiltration (TCUF), the marker clearance (MC) and the net ultrafiltration (netUF) were calculated according to previously described formulas (11). In brief TCUF was calculated from the dilution of the volume marker, by subtracting the initial theoretical IPV from the theoretical IPV. The theoretical IPV is the IPV in the absence of marker clearance and sampling, in which marker clearance equals the disappearance of fluid from the peritoneal cavity. MC was defined as the difference between the amount of dextran 70 instilled and the total amount recovered, divided by the product of dwell time and the mean dextran 70 concentration. Δ-IPP was calculated using the equation: Δ-IPP = IPP2 – IPP1.

Results are expressed as mean and standard deviation (SD) or median and ranges. For comparison of the results of the two solutions in 9 children a Students t-test for paired samples was performed. Correlations were tested using the Spearman rank correlation analysis.

Parameter	Group	Mean	SD	P-value
IPP1	3.86% glucose	11.4	7.0	NS
	Icodextrin	10.6	3.7	
IPP2	3.86% glucose	16.1	6.1	NS
	Icodextrin	12.4	4.5	
TCUF	3.86% glucose	1053	150	<0.001
	Icodextrin	278	153	
MC	3.86% glucose	348	241	0.04
	Icodextrin	150	140	
NetUF	3.86% glucose	857	125	<0.001
	Icodextrin	156	147	
Time on PD	3.86% glucose	27.6	35.9	NS
	Icodextrin	35.4	40.9	
Age	3.86% glucose	5.7	3.4	NS
	Icodextrin	6.2	3.3	

Table 2. Student-t test for paired samples. Comparison of transport parameters obtained during a 3.86% glucose peritoneal equilibration test (PET) and an icodextrin PET in 9 children on chronic PD. IPP (cmH_2O) = intraperitoneal pressure, TCUF (ml/1.73 m^2) = transcapillary ultrafiltration, MC (ml/1.73 m^2) = marker clearance, netUF (ml/1.73 m^2) = net ultrafiltration , time on PD (months).

Results

IPP measurement

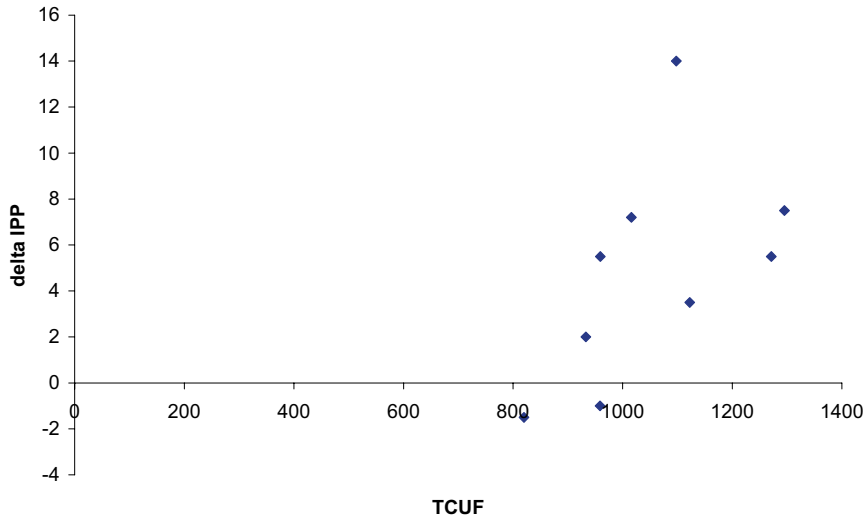
Patient characteristics and results of the IPP measurements are given in table 1. The mean IPP was 12 ± 6.5 cmH_2O in a group of 30 children. There were no relations found between the IPP and age, duration of PD, BSA and BMI. There was no significant difference in IPP measured in boys and girls.

The median inflow volume used was 1188 ± 57 mL/m² BSA, while the median fill volume for the chronic routine prescription was 902 ± 134 mL/m² BSA.

Influence of different dialysis fluids on IPP

Results of the measurement of IPP and fluid parameters obtained during a PET with 3.86% glucose and icodextrin in the 9 children who underwent both PETs are given in table 2. IPP1 was not significantly different between the PET performed with glucose 3.86% and the one performed with icodextrin. IPP2 was also not significantly different between the 2 solutions. The fluid parameters TCUF, MC and netUF were significantly higher for the 3.86% glucose group. In the 3.86% glucose PET IPP1 had a negative correlation with

1A



1B

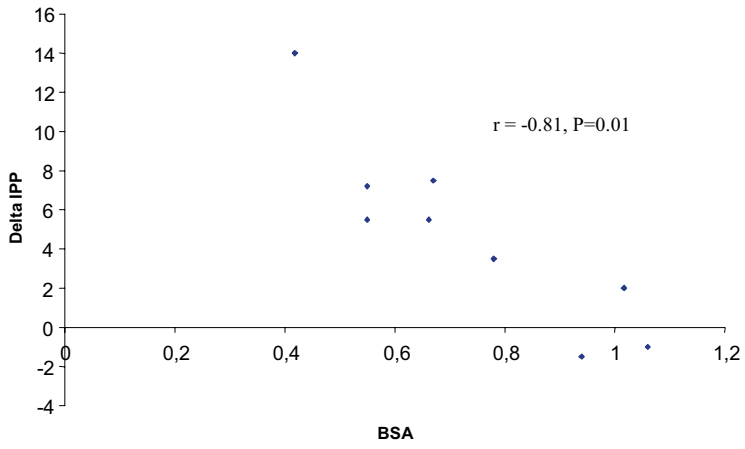
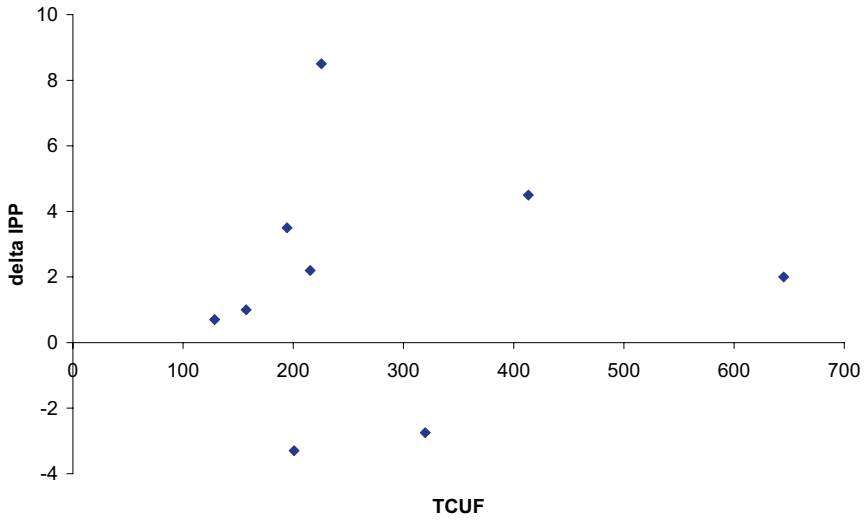


Figure 1. Spearman rank correlations between Δ-IPP and transcapillary ultrafiltration (TCUF) and body surface area (BSA) using two different test solutions (3.86% glucose and 7.5% icodextrin) during a Peritoneal Equilibration Test (PET) in 9 children. (A) Relation between Δ-IPP and TCUF during a 3.86% glucose PET (B) Relation between Δ-IPP and BSA during a 3.86% glucose PET,
Delta-IPP (cmH_2O) = Δ-IPP = IPP2-IPP1, TCUF (ml/1.73 m^2), BSA (m^2)

MC (r = -0.91,P < 0.01). No relation was found with TCUF, UF and age. No significant change of Δ-IPP was found in relation to duration of PD, UF and MC. A significant change of Δ-IPP was found in relation to TCUF (r= 0,67, P = 0.05) and BSA (r = -0.81, P = 0.01) (figure 1a, 1b). No correlation was found between BSA and UF.

1C



1D

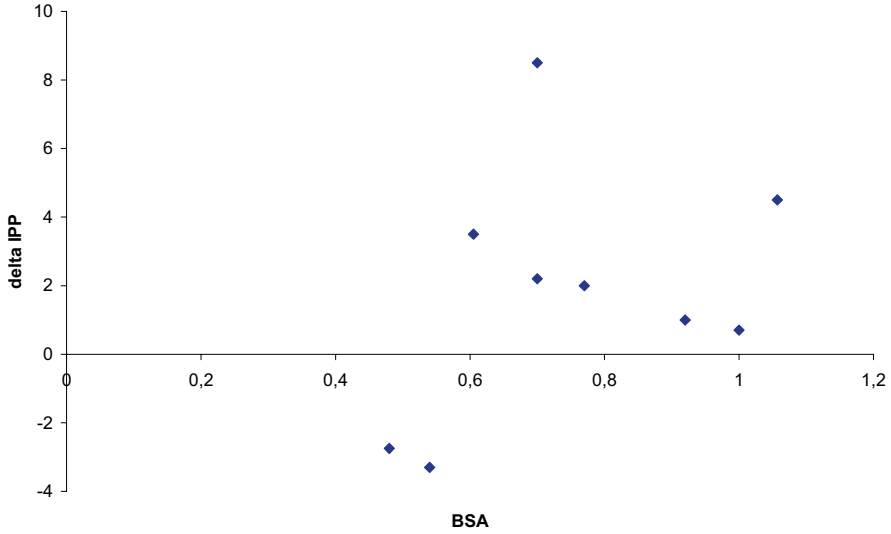


Figure 1.
(C) Relation between Δ-IPP and TCUF during an icodextrin PET
(D) Relation between Δ-IPP and BSA during an icodextrin PET.

In the icodextrin group no relation was found between IPP1 and MC (r = -0.18, P = 0.64), TCUF, UF and age. No correlations were present between Δ-IPP and duration of PD, TCUF (figure 1c), UF, MC or BSA (figure 1d).

None of the patients experienced any allergic reaction or peritoneal pain due to the addition of dextran 70.

Discussion

In a number of studies Fischbach et al. have studied the IPP in children on chronic PD (1-4, 6,7). They studied the influence of several parameters on IPP (age, posture, IPV, body size and BMI) and indicated that IPP overall appears to be an individual parameter. They also brought attention to the usefulness of IPP as a tool to optimize individual dialysis prescriptions in children.

Measurement of the total pore area over diffusion distance ($A_0/\Delta X$) of the peritoneal membrane -also called the peritoneal exchange area- has proven to be a reliable indicator of peritoneal membrane function (12). The $A_0/\Delta X$ is related to the area of the peritoneum that is in contact with dialysis fluid and consequently the intraperitoneal fill volume dynamically affects $A_0/\Delta X$ (13,14). As IPP measurement can be used as an objective assessment of fill volume tolerance (7), IPP measurement in combination with determination of $A_0/\Delta X$ will allow to create an optimal individualized prescription of a dialysis regimen.

The aim of this study was to establish the IPP in children in a larger patient group and examine the influence of dialysis fluids containing different osmotic agents on IPP. The IPP was measured in a supine position with 1200 ml/m² BSA of a 1.36% glucose solution in 30 children on chronic peritoneal dialysis. The values of IPP were in the same range as those reported in literature, obtained in the same age group, with similar fill volumes and with the same body position (7). It should be realized that bicarbonate buffered dialysis fluids, having a more biocompatible pH and containing less glucose degradation products will give rise lower IPP's (10). This positive effect of the newer dialysis fluids probably is thanks to the occurrence of less inflow pain (10). In our study none of the children complained of inflow pain. However we did not measure pain perception by use of a visual pain scale. It also should be realized that an increase of IPV induces an increase in the peritoneal surface area in contact with the dialysis fluid. Chagnac et al. observed a significant increase of this "wetted" area after a 50% increase of the IPV (14). In our study we used an IPV, which was approximately 28% higher than the chronic routine prescription. We were not able to demonstrate a difference in IPP between genders as was seen in a group of 81 adult patients (9), and in a group of 17 pediatric patients (8). In both study groups the IPP was approximately 2 cmH_2O higher in males compared to females, and it was concluded that physical characteristics as gender and muscle tone are determinants of IPP (9). Based on our results it can be concluded that gender plays no major role in determining IPP in pediatric patients. Another relation that was not found in our study was the relation between BMI and IPP. The results of previous studies performed in children (8) and adults (9) showed an interesting relation between body size and IPP, which implied the need to look at body size for optimization of fill volume prescription. The variation in BMI in our study was, however, small.

The second part of our study describes the effect of different osmotic agents on IPP during a 4-hour dwell. IPPs were measured at 2 consecutive time points during a PET performed with icodextrin and a PET performed with 3.86% glucose as a test solution. In both PETs IPP1 was

measured at the end of a rinsing procedure with 1.36% glucose (1200 ml/m² BSA). Because 1.36% glucose exerts only a small osmotic effect it can be concluded that IPP1 is not influenced by an unintended increase in volume. Measuring IPP1 under the same circumstances also allowed us to detect changes in patient conditions, which possibly could have occurred in the time that elapsed between the two PETs. Since IPP1 was not significantly different in a paired samples test, we assumed that no important changes in patient conditions had occurred. The IPP plays an important role in the fluid movement from the peritoneal cavity into the body. Previous studies have shown that this fluid movement is mainly dependent on intraperitoneal hydrostatic pressure and relatively independent on osmotic pressure (15,16). Durand et al. observed in adult patients that ultrafiltration was influenced to a great extent by the intraperitoneal pressure (17). This is illustrated by our data showing a strong negative correlation between IPP1 and the MC during the 3.86% glucose PETs while during the icodextrin PETs there was no relation found between IPP1 and MC. This can be explained by difference in fluid kinetics between 3.86% glucose and icodextrin. Using a 7.5% icodextrin solution there was a significantly lower netUF after the 4-hour dwell period compared to netUF obtained with 3.86% glucose. This has also been reported in adult patients (18). As a consequence the hydrostatic pressure will not rise sufficiently to influence fluid movement from the peritoneal cavity into the body using icodextrin during a 4-hour dwell period. As icodextrin exerts its osmotic effect for up to 12 hours, it will be interesting to evaluate IPP after a 12-hour dwell with icodextrin. The correlation present between Δ-IPP and BSA during the glucose 3.86% PETs implies that there is a higher increase in IPP during a 4-hour dwell with glucose 3.86% in patients with a smaller body size. These data confirm results obtained in a study in 14 pediatric patients that showed an initial increase in IPP secondary to an increase in IPV (IPV). The increase in IPP was more prominent in younger children (7). The absence of this correlation during the icodextrin PETs is explained by the smaller increase in IPV. It is not very likely that the differences are due to the tendency of higher IPPs with acidic dialysis fluids as compared to IPPs measured with more neutral dialysis fluids (10) since both dialysis fluids we used in this study have an acidic pH (icodextrin:5.2 and glucose 3.86%: 5.5). A study in adult patients showed that there is no relationship between IPP and the subjective discomfort degree experienced by patients, although the mean discomfort experienced was higher with larger dialysate volumes (9). As a consequence it seems important to observe the individual degree of comfort using a larger dialysate volume of a solution with a high glucose concentration, especially in small children.

It is concluded that IPP measured in a relatively large pediatric group of 30 patients are similar to those reported in these studies performed in smaller patient groups with the same fill volume. Due to the difference in fluid kinetics between icodextrin and 3.86% glucose the two solutions have a different effect on the change of IPP during a 4-hour dwell period. When using an osmotic agent that induces a rapid ultrafiltration the increase in IPP is inversely related with BSA. When using an osmotic agent that induces a slow but sustained ultrafiltration IPP hardly increases after a 4-hour dwell and no relations are found with fluid kinetics or patient characteristics. Further studies are needed to evaluate such relations after a longer dwell.

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Part III

Intraperitoneal drug administration

3

Long-term effectiveness of intraperitoneal erythropoietinin children on NIPD by administration in small bags

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Introduction

Renal anemia in pediatric patients treated with chronic peritoneal dialysis can be effectively treated with erythropoietin (EPO) (1-3). Until now, subcutaneous injection has been the most often used mode of administration (3,4). Intraperitoneal administration has proven to be an alternative method of treatment (1,2,5). This application route is preferred because subcutaneous injections may be painful and frightening for the child. The major disadvantage seems to be the need for higher maintenance doses (1,4). In the present study we describe the results of a long-term therapeutic study in which EPO was administered in 50 mL of dialysis fluid.

Patients and methods

The study population consisted of 20 children (8 girls and 12 boys) with a median age of 3.8 years (range 0.9-14). All were treated with nightly intermittent peritoneal dialysis (NIPD) during the study period and had been treated for a median period of 5 months (range 0-108 months).

Patients started with a weekly dose of 200 units of EPO (Eprex, Janssen-Cilag) per kilogram bodyweight. The EPO was administered three times per week in dialysis bags that were made especially for this purpose (Baxter BV, Utrecht, The Netherlands). These bags contained 50 mL of NaCl 0.9% solution. The parents injected the hormone into the bags themselves. The bags were instilled after complete drainage of the abdomen for a 10- to 12-hour dwell during the day.

The target hemoglobin level was 104-112 g/L. Dosage was adjusted every two months; EPO dosage was increased by 75 U/kg/week until the target level was reached. Dosage was decreased by 75 U/kg/week if the Hb concentration exceeded 112 g/L. Hemoglobin, hematocrit and the number of reticulocytes were assessed every 4 weeks. Serum ferritin levels and transferrin saturation were assessed every two months, and iron supplementation was prescribed in the case of iron deficiency (serum ferritin below 100 mg/L; transferrin saturation below 20%).

Results

Patients were treated with EPO administered in 50 mL of dialysis fluid for a median period of 10 months (range 3-12 months).

The median Hb level was 94.4 g/L at the start of the study and increased to 105.6 g/L (range 80-134.4) and 110.4 g/L (range 89.6-131.2) after 3 and 12 months of treatment, respectively (Figure 1).

The median EPO dosage was 200 U/kg/week at the start of the study and remained stable during the study period (Figure 2). During the last 2 months of the study period, the range of EPO dosage was very broad. This was due to a very high dosage of 715 U/kg/week in 1 child. This high dosage was given after a rapid decline in the hemoglobin concentration

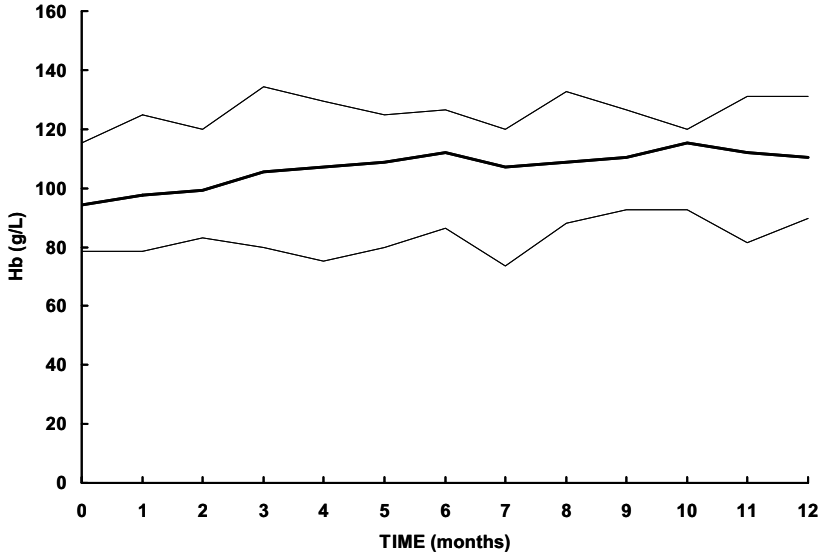

Figure 1 Minimum, median and maximum hemoglobin level (g/L) during intraperitoneal administration of erythropoietin in 50 ml of dialysis fluid. N: number of patients.

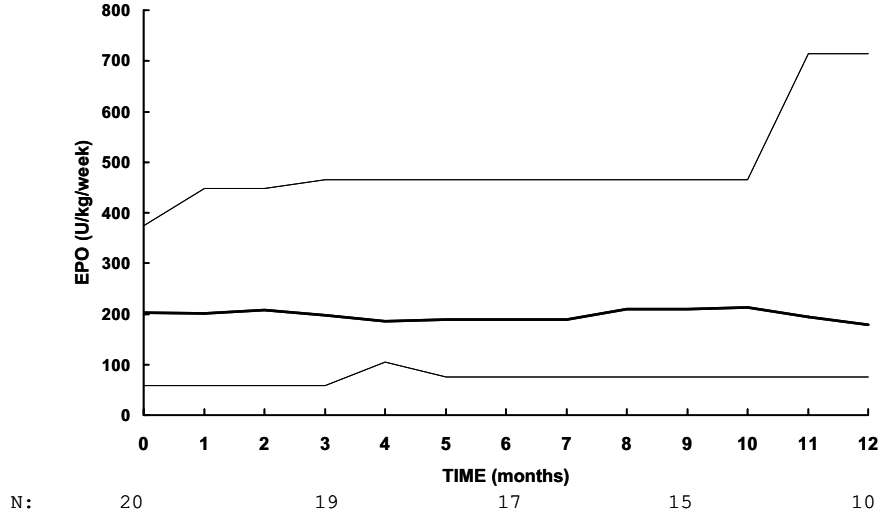

Figure 2 Minimum, median and maximum erythropoietin dosage with intraperitoneal administration of erythropoietin in 50 ml of dialysis fluid. N: number of patients.

from 108.8 g/L to 92.8 g/L, during a period of peritonitis.

Eighteen of 20 children received oral iron supplementation (2-3 mg/kg/day) because of iron deficiency.

The peritonitis incidence during the study period was 1 episode every 11.2 patient months.

Discussion

The main disadvantage of intraperitoneal administration of EPO seems to be the need for higher maintenance doses. However, it was established that the absorption of EPO after intraperitoneal administration is similar to absorption after subcutaneous administration if the EPO is added to a small volume (50 mL) of dialysis fluid (2,5,6).

The present study describes the results of a long-term therapeutic study in a study population of 20 children. The median EPO dosage remained stable throughout the study period and was 179 U/kg/week after 12 months.

The results of this study demonstrate that the intraperitoneal administration of EPO in 50 mL saline leads to an effective treatment of renal anemia. Maintenance doses are similar to those when using the subcutaneous administration route (3). There have been recent studies in which awareness of the possibility of sufficient absorption of EPO was expressed (4,7) and positive findings have also recently been reported(8,9).

A former study of our group showed no relationship between intraperitoneal EPO and an increased risk of peritonitis (1). During the study period, no problems occurred with intraperitoneal administration. The parents did not experience an increase in the burden placed on them. In all our patients, dialysis adequacy (Kt/V^3 2.2) was obtained without the need for daytime dwells, thus allowing daytime EPO therapy.

We think that intraperitoneal EPO should replace the subcutaneous administration of this hormone in pediatric patients.

ACKNOWLEDGEMENTS

Baxter BV, Utrecht, The Netherlands is greatfully acknowledged for supplying the small dialysis bags.

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4

Effective treatment of peritoneal dialysis-associated peritonitis in children with cefazolin and ceftazidime

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Abstract

Objective: To evaluate the use of the combination of cefazolin and ceftazidime for initial treatment of PD related peritonitis in pediatric patients.

Design: Retrospective nonrandomized study.

Setting: Pediatric dialysis units of the University Medical Center of Utrecht and Nijmegen, The Netherlands.

Patients: 40 children (median age 5.4 years) who were treated with PD during the study period of 4.5 years.

Interventions: All 50 episodes of peritonitis that occurred during the study period were evaluated by review of medical records. Patients were given intraperitoneal ceftazidime 500 mg/L dialysis fluid, and cefazolin 500 mg/L as a loading dose, followed by a maintenance dose of ceftazidime 125 mg/L and cefazolin 100 mg/L, intraperitoneally, 4 times daily. Antibiotics were continued for 14 days.

Results: After identification of the causative microorganism, one of the antibiotics was discontinued in 34 cases, and the antibiotic schedule was adapted in 2 cases. All cases were initially cured within 3 days. In 5 cases (10%) there was a peritonitis with the same organism recurring within 2 weeks after completion of treatment. There were 4 cases of PD-related peritonitis caused by pseudomonas, all of which were cured.

Conclusions: The antibiotic combination of cefazolin and ceftazidime is effective for the initial therapy of PD-related peritonitis in children. The toxic complications of aminoglycosides are avoided with this combination.

Introduction

The most recent international treatment guidelines regarding peritoneal dialysis (PD)-associated peritonitis in children propose the use of continuous therapy with a combination of intraperitoneal (IP) cephalosporin and aminoglycoside (1).

The use of aminoglycosides has to be questioned, because of its toxicity profile (2,3). When 2 of our patients suffered hearing loss following tobramycin given in the recommended dose, we decided to replace tobramycin by ceftazidime, a third-generation cephalosporin. The present study evaluates our experience with this combination of a first- and a third-generation cephalosporin in the treatment of peritonitis in pediatric patients on PD.

Patients and methods

We reviewed all cases of peritonitis in children on PD during the 4.5-year period spanning 1 September 1994 to 1 April 1999. The medical records of 40 children (24 boys, 16 girls; median age 5.4 years, range 3 months to 18.9 years) were studied. The patients had been treated for a total of 665 patient-months, with an average of 15 dialysis treatment months (range 1-40 months) per patient. Thirty-three children were treated with automated PD (nocturnal intermittent PD) , 6 with continuous ambukatory peritoneal dialysis (CAPD), and 2 children switched from CAPD to automated PD during the study period.

Peritonitis was defined as cloudy peritoneal effluent associated with an increased number of white blood cells (>100/mm^3) and/or micro-organisms in the dialysate effluent demonstrated by culture and/or associated with abdominal pain (4). Cases that did not match the definition, cases with asymptomatic cloudy peritoneal effluent showing more than 15% eosinophils on a differential cell count (eosinophilic peritonitis) (4), and cases that were not initially treated with a first- and a third-generation cephalosporin were excluded from analysis.

Resolution of peritonitis was defined as disappearance or improvement of peritoneal dialysate cloudiness and clinical symptoms within 3 days after the initiation of antibiotic therapy. Recurrence was defined as a peritonitis with the same organism recurring less than 2 weeks after treatment completion.

When peritonitis was diagnosed, patients were switched to standard CAPD. Antibiotic therapy was started with IP ceftazidime 500 mg/L and cefazolin 500 mg/L as a loading dose, followed by a maintenance dose of 125 mg/L ceftazidime and 100 mg/L cefazolin IP, 4 times daily, for a 14-day period. As soon as culture results were available, therapy was evaluated. Depending on the sensitivity of the causative microorganism, therapy was adjusted and one of the antibiotics was discontinued.

Culture techniques were slightly different in the two university hospitals where the study was performed. For culture of dialysis fluid, 10 mL of dialysis fluid was centrifuged and smeared on a blood agar plate and a MacConkey agar plate in one hospital; in the other hospital, 3 times 15 mL dialysis fluid was centrifuged and put, respectively, on 1 blood agar plate, 1 chocolate agar plate and 1 serum broth and cysteine agar plate.

Causative organism	Episodes (n)
Staphylococcus aureus	9
S. epidermidis	7
Pseudomonas sp	4
Streptococcus sp	6 (Strept. Viridans 3; Hemolytic group A 2; Strept. Sanguis 1)
E.coli	2
Enterococcus	1
Enterobacter	1
Haem. Influenzae	1
Corynebacterium	1
Acinetobacter	3
Klebsiella oxitoca + Stenotrophomonas maltophilia	1

Table 1. Organisms isolated from the dialysate of 27 children during 50 peritonitis episodes

Results

During the study period, 27 of our patients had 50 episodes of peritonitis that were initially treated with a first- and a third-generation cephalosporin. Thirteen patients remained free of peritonitis during the study period. The incidence of peritonitis was 1 episode every 11.9 patient months.

A variety of organisms caused the peritonitis; Table 1 lists the causative organisms. Peritoneal fluid cultures were negative in 13 episodes (26%); the first method described above had a rate of 26.9% of sterile cultures, and the second method had a rate of 23.3 %. This difference was not significant (c^2=3.18, p= 0.07). There was one case in which no culture was done.

After identification of the causative micro-organism, one of the antibiotics was discontinued in 34 cases. In all but one case, the causative micro-organism was susceptible to either ceftazidime or cefazolin. In all 16 cases caused by staphylococci, there was no methicillin resistance. The antibiotic schedule was adjusted in two cases. Ceftazidime was replaced by cotrimoxazole in a case caused by Klebsiella oxytoca and Stenotrophomonas maltophilia, because of resistance of Stenotrophomonas maltophilia to ceftazidime and cefazolin. Based on signs of sepsis at clinical presentation, intravenous instead of IP administration of ceftazidime was used during the first 2 days of treatment in a case of peritonitis caused by pseudomonas. In all 50 peritonitis episodes, cloudiness of peritoneal fluid and clinical symptoms improved within 3 days after the initiation of antibiotic therapy. There were 5 recurrences of peritonitis with the same organism less than 2 weeks after the completion of treatment of peritonitis (1 Staphylococcus aureus, 2 S. epidermidis, 1 enterobacter, 1 corynebacterium). These relapses were treated in exactly the same way as the primary

episodes and all were cured. There were no new relapses. This means that the combination of ceftazidime and cefazolin was effective in 90% of the episodes.

Discussion

The international treatment guidelines regarding peritoneal dialysis-associated peritonitis in children propose the use of a combination of IP cephalosporin and aminoglycoside (1). The use of aminoglycosides has to be questioned because of their toxicity profile (2,3). Aminoglycosides have cochlear and vestibular ototoxic effects, which are in part responsible for sensorineural hearing loss in pediatric patients with chronic renal failure (2). They also seem to increase the rapidity of decline in residual renal function in peritoneal dialysis patients; residual renal function is an important independent predictor of technique survival in peritoneal dialysis therapy (3).

We evaluated our experiences with the combination of cefazolin and ceftazidime as initial treatment of peritoneal dialysis-associated peritonitis in 27 children (50 episodes). The use of this combination is in line with the current recommendation for initial treatment of peritonitis of the International Society for Peritoneal Dialysis (ISPD) year 2000 guidelines for adult patients (5).

Ceftazidime is a third-generation cephalosporin with an antibacterial profile against gram-negative organisms that is similar to the antibacterial profile of aminoglycosides, but with less-serious side effects. Compared to the other third-generation cephalosporins, ceftazidime has similar activity against Enterobacteriacae and better activity against pseudomonas.

The incidence of peritonitis in our study population falls within the range of other pediatric studies (6,7). Initial treatment with a combination of ceftazidime and cefazolin has an acceptable success rate. Schaefer et al. recently published a success rate of 86.1% with a combination of glycopeptide and ceftazidime (7). Even though we have to take into account that his definition of relapse was different from ours (recurrence within 4 weeks instead of 2 after completion of treatment), our results are comparable. The use of glycopeptides has to be questioned because of its ototoxic and nephrotoxic effects. Initial therapy with cefazolin and levofloxacin gave improvement of symptoms at 48 hours in 94% of all episodes of peritonitis in adult patients on peritoneal dialysis (8).

Adult patients presenting streptococcal peritonitis seem to have a considerably higher peritonitis rate than other patients (9). In our pediatric patients, this was not the case. Our cases also did not follow a severe course, in contrast with some cases reported in the literature (10,11). The incidence of streptococcal peritonitis in our population is high (13 %) compared with other studies (3-6%) (7,11,12).

The incidence of sterile cultures was high in our analysis, even though this incidence is similar to results described in the literature (7,13). A possible explanation may be the use of relatively small volumes of dialysate for culture. The recently published guidelines for adults recommend the use of larger volumes (≥ 50 mL) to maximize bacterial recovery rates (5).

One of the advantages of using ceftazidime is its good activity against pseudomonas. In our population, we had a succes rate of 100% in pseudomonas peritonitis (4 cases) using ceftazidime monotherapy. Good results are reported with the combination of ceftazidime and ciprofloxacin in the treatment of pseudomonas peritonitis in adult patients on peritoneal dialysis (14,15). Even though our study group is small, we think initial treatment with ceftazidime is a good possibility for treatment of Pseudomonas peritonitis.

A possible disadvantage of the combination of cefazolin and ceftazidime is the resistance of methicillin-resistant Staphylococci to this combination. If these micro-organisms are diagnosed or suspected, the antibiotic treatment regimen has to be adjusted.

The present study describes the continuous treatment with the combination of a firs-t and a third-generation cephalosporin. Based on recent publications showing good effects with the intermittent administration of these antibiotics, the combination described in this study might also be suitable for discontinued therapy. This will be advantageous to the majority of pediatric patients that are on a nocturnal intermittent PD dialysis regimen and do not have to switch to CAPD. The combination of glycopeptides and ceftazidime showed good effects with intermittent administration (7) and another study showed effective serum concentrations (greater than the minimum inhibitory concentration over 48 hours) with intermittent dosing of cefazolin (16).

We conclude that initial treatment with IP cefazolin and ceftazidime is effective in peritoneal dialysis-associated peritonitis in children. Side effects of aminoglycosides are avoided with this combination. Also, the use of vancomycin as an initial therapy is avoided.

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Part IV

Complications of peritoneal dialysis

5

Gastrointestinal motor function in children treated with peritoneal dialysis

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Introduction

Continuous ambulatory peritoneal dialysis (CAPD) and nightly intermittent peritoneal dialysis (NIPD) in young children with end-stage renal failure are often associated with feeding disturbances such as anorexia, nausea and vomiting. These feeding disturbances are likely caused by chronic renal failure and its treatment.

Because little is known about the mechanism underlying feeding disturbances in young children treated with peritoneal dialysis we examined the existence of a pathological gastroesophageal reflux (GER) and quantified intestinal passage by measuring the mouth-to-caecum transit time (MCTT) in young children treated with peritoneal dialysis.

Patients and methods

After obtaining written informed consent from each patient's relatives, the MCTT and the presence of pathological GER were evaluated in children treated with peritoneal dialysis. All children had end-stage renal disease and were without prokinetics or other drugs with known influence on gastrointestinal function. This study was approved by the local ethics committee.

In 8 children treated with CAPD (four daily exchanges of 40 mL/kg; mean age 5.0 years, range 0.2-9.6 years) the MCTT was investigated by a lactulose hydrogen breath test, using a Lactoscreen (Hoekloos, Schiedam, The Netherlands) as described by Van der Klei et al. (1). None of the patients had feeding disturbances. Basal H_2 expiration was assessed after a 9-hour fast during which patients received their normal dialysis prescription. The MCTT was recorded according to standardized methods; the normal values for MCTT were taken from the study by Vreugdenhil et al. (2).

The presence or absence of pathological GER was also assessed in 8 children (mean age 5.6 years, range 0.8-14.7 years) by 24-hour pH monitoring. Feeding disturbances were present in 6 patients. Five patients were being treated with CAPD (four daily exchanges of 40 mL/kg) and 3 patients were being treated with NIPD (nightly exchanges of 40 mL/kg). The pH probe was a flexible glass electrode (type Lot 440-M4, Ingold/Mettler, Solthurn, Switzerland). The probe was introduced transnasally and located at the third vertebra above the diaphragm, according to Vandenplas (3). Localization was controlled by radiography .

In this study we considered the reflux index (RI). Reference data were obtained from Vandenplas et al. (3,4). They found the RI, (the sum of the periods with a pH < 4 , expressed in percentage of time of the total investigation time) a highly reliable parameter for documenting reflux in children. The upper limits for normal RI are 9.3 % for children younger than 1 year of age and 6.5 % for older children, assuming that, after 1 year of age, the physiologic incidence of GER in children is comparable with that in adults (5).

During both the MCTT and the pH evaluation, patients were fed normally (no supplemental tube feeding),executing normal activities, in their typical feeding position. CAPD

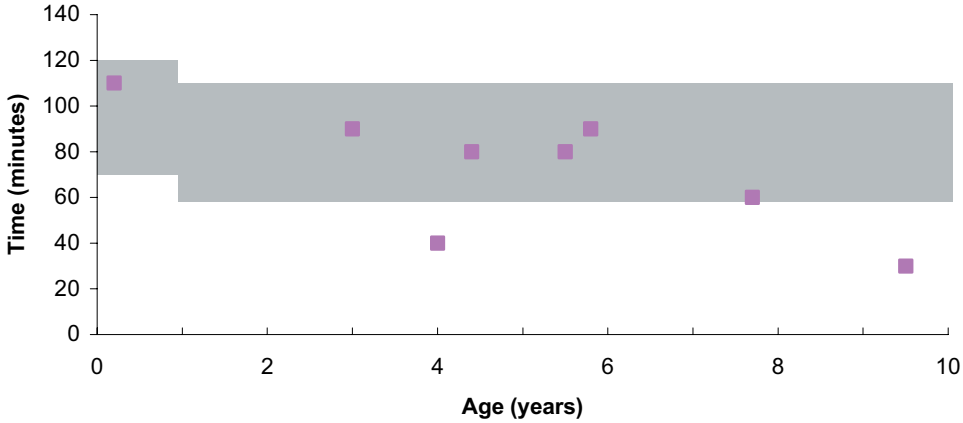

Figure 1 Mouth to caecum transit time in 8 children treated with CAPD. Normal ranges are indicated by the shaded area.

patients received their typical dialysis prescription, while the abdomen of NIPD patients was filled with 40 mL/kg dialysate during the evaluation.

Results

The MCTT was normal in 6 of 8 patients (Figure 1); in 2 children, the hydrogen peak occurred early (after 30 and 40 minutes respectively).

Table 1 shows the results of the 24-hour pH monitoring. One of 8 patients (Patient 8) showed a mild pathological GER.

Discussion

A relatively small number of studies have been published on gastrointestinal function in children with chronic renal failure. Gastric dysrythmias, delayed gastric emptying and gastroesophageal reflux have been reported to play an important role in feeding disturbances (5-9).

In our study the MCTT was not prolonged. The early increase in breath hydrogen in 2 patients may indicate bacterial overgrowth, but there were no clinical symptoms (such as diarrhoea) of bacterial overgrowth. In this study population, the presence of dialysis fluid in the abdomen did not seem to lead to inhibition of intestinal passage, as has been reported in adult patients (10).

The results of the 24-hour pH monitoring demonstrate that there was no pathological GER in any but 1 patient. The slightly increased RI in this patient was associated with a period of emotional distress during which the esophageal pH fell below 4. These results are in strong contrast with the results of other studies , which report the presence of pathological GER in a large percentage of children with chronic renal failure but not in children who were not treated with dialysis (5,6). The results of the present study may suggest that

Patient	Sex	Age (years)	CAPD/NIPD	Reflux index (%)
1	M	7.0	CAPD	6.0
2	M	2.0	NIPD	6.2
3	F	0.8	NIPD	4.8
4	M	4.8	CAPD	3.0
5	M	9.1	NIPD	0.8
6	F	1.5	NIPD	2.6
7	F	14.7	CAPD	1.2
8	F	4.6	NIPD	7.3

Table 1. Results of 24 hour pH recordings.
CAPD = continuous ambulatory peritoneal dialyis;
NIPD = nightly intermittent peritneal dialysis

peritoneal dialysis does have a beneficial effect on gastrointestinal motility.

In conclusion, the feeding disturbances in our patients are not caused by a pathological GER or delayed intestinal passage. The presence of dialysis fluid in the children's abdomen did not influence the results.

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6 Local fibrinolytic therapy with urokinase for peritoneal dialysis catheter obstruction

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Abstract

Objective: Obstruction of the peritoneal dialysis (PD) catheter is a well-known clinical problem. During stable PD, hypofibrinolysis occurs resulting in fibrin deposits, which may lead to subsequent obstruction of the catheter. Local fibrinolytic therapy with a plasminogen activator, such as urokinase which activates the conversion of inactive plasminogen to active plasmin, enhances the degradation of fibrin and may lead to dissolution of the fibrin clot. The aim of the study was to retrospectively evaluate the effect of local fibrinolytic therapy with urokinase on PD catheter obstruction.

Subjects: The study group consisted of 17 children on PD (8 boys, 9 girls) with a mean age of 7.0 years (range 0.2 – 16.0). One child presented twice with an obstructed catheter.

Methods: After catheter obstruction (inflow, outflow, or both) 15,000 IU Urokinase was injected into the catheter which was subsequently clamped for 1 hour. PD was restarted immediately.

Results: A positive effect of urokinase therapy was seen in 9 out of 18 obstructions (50%). Catheter obstruction associated with peritonitis was observed in 5 children. All of them were successfully treated with urokinase (100%).
Obstructions occured either early (within two weeks after catheter implementation), or late (> two weeks after catheter implementation).
Two out of eight early obstructions (25%) were successfully unblocked with urokinase. Of the 10 late obstructions 7 (70%) showed a positive result to urokinase.
Evaluation of the unsuccessful treatment with urokinase therapy showed mechanical obstructions in all of the patients (omentum wrapping in 8 and catheter malpositioning in 1 patient). No systemic side effects of urokinase were seen during treatment.

Conclusion: We conclude that local fibrinolytic therapy with urokinase is a safe procedure and an effective treatment for all obstructed PD catheters, except for catheters obstructed by mechanical causes. Mechanical obstructions tend to occur early (< 2 weeks after implementation). Obstructions associated with peritonitis occur relatively late (> 2 weeks after implementation).

Introduction

Catheter obstruction is a serious complication of peritoneal dialysis (PD) in dialysis-dependent patients. Eight to fifteen percent of both adults and children on PD present with a malfunctioning catheter sometime during dialysis [1-3]. This problem can be due to either mechanical obstruction, such as catheter malposition or omentum wrapping, or to obstruction of the catheter lumen, caused by fibrin deposits.

As previous studies reported, intraperitoneal hypercoagulation and a relative hypofibrinolysis have been observed during stable PD, resulting in an accelerated fibrin turnover [4].

During peritonitis, the imbalance of the fibrinolytic system appears even more marked [5]. Fibrin deposits may subsequently obstruct the PD catheter. Local fibrinolytic therapy with a plasminogen activator, such as urokinase which activates the conversion of inactive plasminogen to active plasmin, enhances the degradation of fibrin and may dissolve the obstructing fibrin clot.

In this study, we retrospectively (September 1987 to May 2001, a period of 14 years) evaluated the effect of fibrinolytic therapy with urokinase in children with PD catheter obstruction.

Patients and Methods

The study population comprised 17 children (8 boys, 9 girls) receiving PD for end-stage renal failure (ESRF). The median age was 7.0 years (range 0.2 to 16.0 years). Mean duration of PD was 7.7 months (range 0 to 69 months). All children presented with an obstructed catheter. One child experienced two episodes of catheter obstruction. Causes of ESRF and clinical data of the children are summarised in Table 1.

In 5 children, peritonitis occurred within 1 month prior to PD catheter obstruction. Peritonitis was defined as cloudy peritoneal effluent associated with an increased number of white blood cells (>100/mm3) and/or micro-organisms in the dialysate effluent, demonstrated by culture [6].

Catheter obstructions (inflow, outflow, or complete obstruction) ocurred either early (≤ 14 days after catheter implementation) or late (> 14 days after catheter implementation).

Unblocking the catheter with urokinase was attempted following a published protocol [7]. First, the occluded catheter was manually flushed with 10 ml NaCl 0.9% using a sterile 10 ml syringe. Then 15.000 IU urokinase, dissolved in 5 ml NaCl 0.9% was injected into the catheter, which was subsequently clamped for 1 hour. Afterwards the catheter was flushed with 2 x 10 ml NaCl 0.9%. Peritoneal dialysis was restarted immediately. Urokinase therapy was considered effective if the catheter was unblocked and restored to function.

N	Sex	Age in years	Cause of ESRF	Duration PD (months)	P < 1 month	Obstruction	Weeks since Catheter Insertion	Effect Urokinase
1	M	2.1	TIN	8.1	–	Outflow	32.6	Yes
2	M	0.3	PBS	1.2	+	Outflow	5.4	Yes
3	M	6.1	PUV	7.7	+	Outflow	0.7	Yes
4	F	0.2	Hyperoxaluria	0.0	–	?	0.0	No
5	F	0.2	Hypoplasia	2.1	+	Complete	9.0	Yes
6	F	12.6	HSN	0.3	–	Complete	1.3	No
7	F	5.7	Acro-osteolysis	5.9	–	Complete	24.9	No
8	F	10.2	Unknown	0.3	–	Complete	1.3	No
9	M	14.5	Hypoplasia	8.2	–	Outflow	0.0	No
10a*	F	1.9	Dysplasia	2.5	–	Outflow	11.0	No
10b*	F	2.2	Dysplasia	6.5	–	Complete	17.3	Yes
11	M	14.4	FSGS	69	+	?	89.6	Yes
12	F	12.1	Cystinosis	0.3	–	Outflow	1.6	No
13	M	0.2	Secundary to cardiac disease	0.1	–	Complete	1.0	Yes
14	M	1.0	Dysplasia + TIN	0.1	–	Outflow	4.0	Yes
15	F	14.9	Anti-GBM GN	0.5	–	Outflow	2.0	No
16	M	11.7	Dysplasia	7.2	–	Outflow	31.7	No
17	F	16.0	Unknown	11	+	Inflow	47.7	Yes

* the same child

Table 1: Clinical data of the patients studied. (ESRF = end-stage renal failure; PD = peritoneal dialysis; PBS = prune belly syndrome; TIN = tubulointerstitial nephritis; PUV = posterior urethral valves; HSN = Henoch-Schönlein nephritis; FSGS = focal segmental glomerulosclerosis; anti-GBM = antiglomerular basement membrane; GN = glomerulonephritis)

Results

A positive effect of urokinase therapy was seen in 9 of 18 (50%) obstructions. All five PD catheter obstructions associated with peritonitis were successfully treated with urokinase. In contrast, only 4 of 13 (31%) children without peritonitis responded well to therapy.

Two of eight (25%) early obstructions and seven of ten (70%) late obstructions showed positive results with urokinase. Most (80%) obstructions associated with peritonitis occurred late. Early (25%) obstructions were not associated with peritonitis, except for one occluded catheter, and responded poorly to urokinase treatment.

Successful fibrinolysis was achieved in 5 of 9 outflow obstructions, 2 of 6 complete obstructions and in the only inflow obstruction observed. In two children, the kind of obstruction was not adequately documented; One showed a positive effect to urokinase infusion.

Surgical evaluation of the unsuccessful treatments with urokinase therapy showed mechanical obstructions in all of the children: direct omental adhesions to the catheter (wrap) in 8 children and catheter blocking by the intestine in 1 child. Six of nine mechanical obstructions occurred early. No systemic side effects of urokinase, such as a bleeding tendency, were observed during or after treatmant.

Discussion

Excessive fibrin formation due to hypercoagulation and hypofibrinolysis in PD patients contributes to fibrin clots and subsequent obstruction of PD catheters [4]. During peritonitis, intraperitoneal hypercoagulation increases even more [3,8]. This might explain the increased rate of catheter obstruction during peritonitis and the excellent results to urokinase therapy observed in children with peritonitis in the present study.

Recent unavailability of urokinase on the market underscores the need for a substitute fibrinolytic agent. Tissue plasminogen activator (tPA) probably is an acceptable alternative [9, 10].

In summary, we conclude that local fibrinolytic therapy with urokinase is a safe and effective treatment for PD catheter obstruction. Urokinase should always be administered in obstructions following peritonitis or occurring more than two weeks after catheter implementation. In early obstructions and in children without peritonitis, obstructions are probably caused by anatomical structures, through mechanisms unlikely to respond to urokinase. However, before surgery for an occluded PD catheter is considered, an attempt with intraluminal urokinase should always be made.

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7

Fibrin glue successfully used in peritoneal dialysis catheter leakage in children

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Abstract

Background. Acute renal failure in infants and small children is generally treated with peritoneal dialysis. Immediately after catheter implantation dialysis has to be started. Early dialysate leakage can complicate the effectiveness of dialysis. Fibrin glue applicated in the external part of the tunnel may stop dialysate leakage and prevent surgical intervention. The use of fibrin glue in the treatment of peritoneal dialysis catheter leakage in children was studied .

Methods. Fibrin glue was used in eight children on peritoneal dialysis (age 4 - 57 months) in whom dialysate leakage was seen in the first 24 to 48 hours after catheter insertion. The dialysis volume initially administrated was 20ml/kg body weight. The fibrin glue (1ml) was applied in the external part of the subcutaneous catheter tunnel through the exit site as closely to the cuff as possible. The occurrence of dialysate leakage and complications such as exit-site or tunnel infection and peritonitis were evaluated.

Results. Nine single cuff straight Tenckhoff catheters were implanted in eight children. In five cases no subcutaneous tunnel was created. One child had a catheter replacement due to obstruction of the catheter: on both occasions catheter leakage was seen and treated with fibrin glue. In all eight patients no relapse of dialysate leakage was seen after application of the fibrin glue. During the time of peritoneal dialysis neither exit-site infections nor tunnel infections or peritonitis occurred.

Conclusion, Fibrin glue is a successful, simple and safe substance for the treatment of peritoneal dialysate leakage in infants and small children with acute renal failure treated with peritoneal dialysis.

Introduction

The convenience, simplicity and relative safety have made peritoneal dialysis a frequently used dialytic modality in acute renal failure in pediatric patients (1-3). In the case of acute renal replacement therapy, immediate dialysis following catheter insertion is needed. In contrast to the guidelines on chronic peritoneal dialysis (4), it is not possible to leave the catheter for two weeks in order to allow initial healing. As a consequence peritoneal dialysis catheter leakage may occur, which can complicate the effectiveness of dialysis and also bears the potential risk of infection at the catheter exit-site or tunnel and cuff (5), which may eventually result in catheter removal. Leakage also complicates the calculation of the fluid balance. In those cases where temporary interruption of dialysis and/or reduction of dialysate volumes do not solve the leakage, replacement of the peritoneal catheter is indicated. Fibrin glue applied in the external part of the catheter tunnel may stop dialysate leakage and prevent infections and surgical interventions (6). Fibrin glue is a two component system of solutions of fibrinogen and thrombin. The mixture of these two solutions mimics the final stages of the coagulation cascade. In the presence of calcium ions thrombin cleaves the fibrinogen chains to form fibrin monomers, which then polymerize to produce a physiologic fibrin clot. The fibrin clot degrades in time (10-14 days) by natural fibrinolysis (7).

The aim of this study was to examine the effectiveness of fibrin glue in the treatment of peritoneal dialyisis catheter leakage in infants and children suffering from acute renal failure who were treated with peritoneal dialysis.

Subjects and methods

Fibrin glue was applied in 8 infants and children in whom dialysate leakage was seen in the first 24 to 48 hours after catheter insertion. Patients varied in age from 4 months to 4.5 years. They all suffered from acute renal failure for which they were treated with peritoneal dialysis. The dialysis volume initially administered was 20 mL/ kg body weight. Dialysate leakage was confirmed by a positive glucose dipstick of the leaking fluid. One mL of ready-to-use fibrin glue (Tissucol® Duo 500, Baxter AG, Vienna, Austria) was applied in the external part of the catheter tunnel through the exit site, as close as possible to the cuff. The fibrin glue kit consists of two compartments. One compartment contains an aprotonine solution; aprotinine: 3000 KIG/mL, fibrinogen: 70-110 mg/mL, fibronectin: 2-9 mg/mL, factor VIII: 10-50 U/mL. The other compartment contains a thrombin-$CaCl_2$ solution; thrombin 500 U/mL and $CaCl_2$ 40 µmol/mL. The contents of the two compartments are mixed by means of a special mixing head and subsequently applied with a blunt needle. Desinfection with iodine or alcohol was avoided because of possible interference with the fibrin glue, which will undo its action.

Evaluation for dialysate leakage, exit site or tunnel infections and peritonitis episodes was performed daily after application of the fibrin glue, with a maximum of 60 days.

Results

In our study group of 8 patients in whom peritoneal dialysis catheter leakage occurred within 24 to 48 hours after catheter placement, fibrin glue was applied for 9 times. In 1 child fibrin glue was applied twice, as a catheter replacement was performed due to subsequent obstruction of the catheter by omentum. In all 9 cases no relapse of dialysate leakage was seen after application of the fibrin glue.

The catheters of the study group comprised 9 single cuff, straight Tenckhoff catheters. In 5 cases the catheter was placed straight into the abdominal wall, while in the other 4 cases a subcutaneous tunnel was created. Placement of the catheter occurred according to the preferred method of the surgeon concerned. The patients in the study group were dialysed for a median period of 7 days after treatment with fibrin glue and 1 patient was transferred to chronic peritoneal dialysis.

During the follow-up period after application of the fibrin glue there were no exit site or tunnel infections observed nor were there any peritonitis episodes. There were no other adverse events observed.

Discussion

The application of fibrin glue in the external part of the catheter tunnel is an effective treatment of periluminal catheter leakage in children on acute peritoneal dialysis.

Although continuous renal replacement therapies, such as continuous hemofiltration and continuous hemodiafiltration, are gaining popularity in the treatment of acute renal failure in children (8,9), peritoneal dialysis remains less technology- and labor-intensive and can be utilized in many clinical settings (1-3,10). The most important factors influencing the choice of a dialysis-modality is the indication for dialysis and the overall clinical status of the patient (10).

The use of peritoneal dialysis in acute renal failure generally implicates that the peritoneal dialysis catheter will be used immediately after placement. This increases the risk of periluminal leakage of dialysis fluid, which can complicate the effectiveness of dialysis and increase the risk of infections at the exit site, catheter tunnel and peritoneal membrane (5).

Reports on leakage of peritoneal dialysis catheters vary from 2.6% to 22% in adults (11-14). In peritoneal dialysis in children similar figures are reported (15-17). Generally used treatments for dialysate leakage include lower dialysate volumes, temporary rest from peritoneal dialysis and surgical repair (18).

Fibrin glue has been used in a wide variety of surgical procedures over the last 20 years (7,19,20). It is used for topical hemostasis and sealing. Experiences with the use of fibrin glue in peritoneal dialysis catheter leakage is still limited. Joffe was the first to describe his positive experiences using fibrin glue in 6 adult patients on chronic peritoneal dialysis (6). Sojo et al. demonstrated some good results in preventing dialysate leakage in children by applying fibrin glue at the time of catheter implantation (5). Our study is the first to

report results in a group of children suffering from acute renal failure for which they were treated with peritoneal dialysis. Our data confirm the previous results (5,6), suggesting that the application of fibrin glue is a succesfull method of treating periluminal peritoneal dialysis catheter leakage which prevents the need of catheter replacement and occurrence of infections.

It is concluded that fibrin glue is a succesful, simple and safe substance for the treatment of peritoneal dialysis catheter leakage in infants and children with acute renal failure who are treated with peritoneal dialysis. Fibrin glue prevents the occurrence of infections and the need for surgical intervention. It deserves a major role in treatment of peritoneal dialysis catheter leakage in both adult and pediatric patients.

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Part V

General discussion

General discussion

Children with chronic renal failure who are treated with peritoneal dialysis, are largely dependent on the functionality of their peritoneum as a dialyzing membrane. Although most children will be transplanted, it has to be kept in mind that sooner or later resumption of dialysis will be needed in case of graft failure. The use of glucose containing dialysis solutions and the occurrence of peritonitis episodes are responsible for progressive loss of the peritoneal permeability. The treatment itself is a burden both for the child and his or her parents, which is in part due to frequent subcutaneous drug application.

In the chapters of this thesis several clinical studies have been described that might give better understanding in therapies that will decrease the burden placed on these children, both physical and psychosocial.

The three general issues that are discussed include (1) peritoneal transport with the use of glucose polymer-based dialysis solutions, (2) intraperitoneal drug application and (3) complications of peritoneal dialysis. Possible future investigations will be indicated.

Peritoneal transport with the use of icodextrin

The peritoneal equilibration test (PET) is a well-known method used to assess the peritoneal transport abilities (1). In order to obtain more information on peritoneal fluid transport, the test has been adapted: dextran 70 was added to the test solution as a volume marker. Experiences with this modified and standardized PET, which is also called standard peritoneal permeability analysis, have been described both in pediatric and in adult patients (2–4). When fluid kinetics are corrected for body surface area, this allows for comparison of results between patients. Comparison of peritoneal fluid kinetics between children and adults using standardized test methods show that there are no differences between those two groups (2,3). This implies that the transport characteristics of the peritoneum of both adults and children are basically the same. This was confirmed in chapter 2: fluid kinetics and solute transport for a 3.86% glucose solution were found to be similar in children and adults.

Icodextrin is a dialysis solution containing glucose polymers, which act as a colloid osmotic agent. Because glucose polymers are hardly absorbed, icodextrin is especially effective during long-term dwells. In adult patients extensive experiences using icodextrin have been described. In children however experience using this polymer-based dialysis solution was limited to one study describing sustained net ultrafiltration during long term dwell and a metabolism similar to that found in adult patients (5). No studies were available concerning the fluid kinetics of icodextrin. The most applied mathematical approach of peritoneal transport is the three-pore model as described by Rippe et al (6–8). Based on this model, aquaporins play a minor role in transcapillary ultrafiltration (TCUF) using icodextrin. Analysis of sodium sieving during the first hour of a dwell showed an absence of a drop in the D/P ratio of sodium using icodextrin. A decrease of the D/P ratio was seen using 3.86% glucose. In the presence of an aquaporin mediated water flow the amount of water

transported will exceed the amount of solutes transported. This will cause a dilution of the dialysate. Our results confirm the value of the three-pore model as a model of peritoneal transport. Fluid kinetics of icodextrin were compared with results previously found in adult patients (chapter 1; 9). In spite of the use of standardized test methods, TCUF and marker clearance (MC) were found to be significantly lower in children compared to adults. Net ultrafiltration (NUF) was similar in both groups. As fluid transport while using icodextrin seems to be mainly a result of water transport through the small pores our results suggest that the pediatric study group must have lower small pore area available for transport. We did not find any other indications that support this idea. The results of our study also suggest that the group of children studied had a 3 times higher amount of functional aquaporins. Lai et al. demonstrated an upregulation of aquaporin-1 in cultured human peritoneal mesothelial cells upon exposure to glucose, which is both time- and dose-dependent (10,11). It was not clear how long the effect of glucose lasted. They also speculated that long-term PD might lead to decreased expression of aquaporin-1 caused by denudation of mesothelial cells. An *in vivo* study in rat peritoneal tissue confirmed that expression of aquaporin-1 is upregulated upon exposure to glucose and hyperosmolality (12). In cultured rat mesothelial cells upregulation of aquaporin-1 was attended with an increase in osmotic induced water permeability (12). A recent study showed that aquaporins can be inactivated while they remain on the cell surface, but it is not yet clear which mechanism is responsible for the inhibition (13). Immunohistochemical analysis of human peritoneum showed that expression of aquaporin-1 is correlated with the amount of water transported through the aquaporins after 1 hour after equilibration with 3.86% glucose (14). The differences found in fluid kinetics of icodextrin between the two study groups suggest that the peritoneum of children has another distribution of the three types of functional pores as compared to the peritoneum of adults. This is in strong contrast with the belief that peritoneal transport, and subsequently the distribution of the pores, is the same in children and adults. Nevertheless our study also showed that the clinical efficacy of the aquaporins is similar in children and adults. It could be hypothesized that the differences found in fluid kinetics using icodextrin between the pediatric and the adult study group are a consequence of differences in exposition to different glucose concentrations and/or differences in duration of PD rather than differences in peritoneal composition. Further studies are needed to elucidate the cause of the differences in fluid kinetics of icodextrin between pediatric and adult patients. Recently Smit et al have published a method which enables direct quantification of free water transport, calculated from a single PET. This method will offer a quick possibility to evaluate aquaporin mediated water transport in children and adults (15). Additionally immunohistochemical analysis of the peritoneum of both pediatric and adult patients is indicated, in order to compare distribution and activity of aquaporins.

Adequate peritoneal transport characteristics and fluid kinetics are of major importance for establishing the optimal treatment modality (16,17). The most widely used technique is the peritoneal equilibration test, which utilizes the dialysate over plasma (D/P) concentration for urea, creatinine and the D/D_0 ratio for glucose. Johnsson et al (18) argued that the

unrestricted pore area ($A_0/\Delta x$) is a better indicator to estimate the capacities of a peritoneal membrane of individual patients as compared to the information provided by the PET. This unrestricted pore area is the product of the number of perfused capillaries in contact with the dialysate, the number of pores per capillary, the area of each of these pores (A_0) and the average diffusion distance between blood and dialysate (Δx). It was suggested that the use of the PET should be replaced by the use of the personal dialysis capacity test (PDC), since PET data fail to provide clear information of changes in underlying mechanisms in the peritoneal membrane, like the relative pore distribution and pore size, while PDC data allow for determination of the transport characteristics of the peritoneal membrane in individual patients. Fischbach et al (19) subsequently were able to demonstrate that the unrestricted pore area can also be estimated adequately from PET data, which proves its value as a tool to obtain data on peritoneal transport characteristics, based on our current knowledge of capillary physiology. Therefore it does not seem to be of additional value to change our 6 month routine of performing a PET into performance of a PDC. Further studies are indicated to investigate the usefulness of PDC in a way to minimize the need of nursing time and decrease the burden placed on the children and parents.

One of the parameters that affects the individual area available for transport of solutes and fluid is the fill volume used (20). Fill volume is also one of the determinants of the intraperitoneal pressure (IPP). We demonstrated an influence of different osmotic agents on IPP, which is dependent on the differences in fluid kinetics: an increase in intraperitoneal volume causes an increase in intraperitoneal pressure (chapter 2). In our strive of creating optimally individualized dialysis prescriptions it seems to be of additional value to measure IPP in combination with the personal peritoneal exchange capacity. Although PET is used in many pediatric centers, measurement of IPP in children is still not widely applied. A recent publication might be helpful to increase the application of IPP measurement, since it offers a useful description of how the measurement should be performed and how the values should be interpretated (21). Another major reason for not measuring IPP was a lack of reference values in children, since data available were obtained in only small study groups. Therefore we measured IPP in a larger group of children, under standardized circumstances. We used an intraperitoneal volume of 1200 ml/m^2, which is an appropriate fill volume in terms of tolerance and effectiveness. Application of fill volumes higher than 1200 ml/m^2 will not contribute to a gain in dialysis efficiency, since the unrestricted pore area will not increase any further and higher intraperitoneal volumes will cause an increase in IPP, which will not be accepted by the child (22). Recently it was shown that Physioneal, a new dialysis fluid with a more neutral pH and containing lower concentrations of glucose degradation products as compared to the conventional lactate-buffered dialysis fluids, induces a lower IPP, implying an enhanced fill volume tolerance (23). Randomized studies on peritoneal dialysis outcome parameters will be needed to elucidate the added value of IPP measurements to optimize individual dialysis prescriptions.

Intraperitoneal drug administration

The presence of a permanent catheter into the peritoneal cavity allows for the intraperitoneal administration of drugs. Antibiotics are generally administered intraperitoneally, in case of peritoneal dialysis-associated peritonitis. The most recent guidelines for the initial treatment of peritonitis in adult patients propose the use of a first- and a third-generation cephalosporin (24). We were able to demonstrate that the use of such a combination (cefazolin / ceftazidime) also leads to good results in the treatment of peritonitis in pediatric patients (chapter 4). This combination of cephalosporins avoids the routine use of aminoglycosides, and thus the risk of nephrotoxicity and ototoxicity. In spite of the results we presented in a group of unselected patients, the first edition of treatment guidelines for pediatric patients recommends the use of this combination only in a small selected group of patients with very low risks (25). Although a first-generation cephalosporin will not be efficient against methicillin-resistant organisms, its use is preferred in the light of the emergence of glycopeptide-resistant organisms and the toxic effects of glycopeptides. Our results support the value of the use of a first- and a third-generation cephalosporin as empiric initial therapy. Once culture results and bacterial susceptibilities are known, a glycopeptide can be introduced if necessary. Besides the advantages of cefazolin, which are mentionned previously, this antibiotic also seems to be suitable for intermittent dosing. As most children receive a nocturnal intermittent PD regimen, they need to switch to a CAPD regimen in case of continuous dosing of antibiotics. Intermittent intraperitoneal antibiotic administration will avoid the need to switch to another dialysis regimen. Schaefer et al. are the first to describe good results with intermittent intraperitoneal treatment of peritonitis in children, using a combination of a glycopeptide and ceftazidime (26). Good results have also been reported with the intermittent intraperitoneal administration of cefazolin in adults (27). This suggests that treatment of peritoneal dialysis-associated peritonitis with intermittent intraperitoneal cefazolin and ceftazidime might be an interesting alternative for the continuous administration of this combination in children who receive an intermittent dialysis regimen. Currently our group is investigating the use of an intermittent dosing regimen.

Subcutaneous administration of drugs is painful and psychologically distressing. As a result noncompliance with erythropoietin has been reported for a majority of adult patients, and this also will be the case in pediatric patients. During the last years positive results have been reported with the intraperitoneal administration of erythropoietin in children. It was shown that, when administered in a small amount of dialysis fluid, erythropoietin was very well absorbed (28) and maintenance dosages were similar to those required during subcutaneous therapy (29). We were able to confirm these results for a larger patient group and a longer treatment period (chapter 3). The development of novel erythropoietin stimulating protein (NESP), or darbepoietin alfa, might be of help to increase the compliance. NESP is a hyperglycosylated erythropoietin analogue, containing two extra carbohydrate chains. NESP has a three-fold longer half-life than erythropoietin and therefore is able to maintain hemoglobin levels as effectively and safely as erythropoietin but requires less frequent dosing

(30,31). Since the introduction of NESP to the market it already has gained an important place in the treatment of renal anemia in patients suffering from chronic renal failure (32). Because there are no data available with respect to the intraperitoneal administration of NESP, a randomized comparative study of intraperitoneal administration of NESP and erythropoietin is needed. If once a week administration of NESP will be sufficient, intraperitoneal administration of this drug will be applicable in almost all PD patients, as it will hardly interfere with the acquaintance of good dialysis adequacy.

Another drug that is traditionally administered subcutaneously, and which is used by many pediatric patients with chronic renal failure is recombinant human growth hormone. Treatment of the growth hormone resistance results in improved growth. To achieve this, daily injections are needed. Changing this mode of administration to intraperitoneal would be of help in decreasing the burden placed on the child and his or her caregivers. Positive results have been reported concerning the absorption of intraperitoneal growth hormone (33, 34). Also intraperitoneal administration of growth hormone in prepubertal peritoneal dialysis patients has proven to be effective and well tolerated (34). This suggests that the intraperitoneal route of administration can be preferred in the treatment of short stature among children on peritoneal dialysis. Dialysis adequacy is a major factor of concern with daily intraperitoneal administration of growth hormone. As most children are able to achieve an acceptable dialysis dose with a nightly intermittent dialysis regimen, daily intraperitoneal administration of growth hormone during the daytime will not interfere with dialysis adequacy. However in those patients in need of a daytime dwell for sufficient dialysis adequacy, intraperitoneal administration of growth hormone will be out of reach.

Complications of peritoneal dialysis

Children with chronic renal failure often suffer from anorexia and sometimes vomiting. Although little research has been performed on the gastroenterological aspects of chronic renal failure in children, impaired gastric emptying appears to play a role in the pathogenesis of these gastrointestinal symptoms. Gastric emptying in children is difficult to evaluate properly. The main reason is the lack of safe and non-invasive methods to measure gastric emptying in children: intubation studies are invasive and time consuming, radioscintigraphic methods cause a radiation burden and ultrasonographic evaluation is largely dependent on the experience of the investigator. The ^{13}C octanoic acid breath test, a new non-invasive breath test, offers a reliable alternative with a non-radioactive character. The test has been adapted for infants and children (35,36) and has an excellent reproducibility (37). In chapter 5 we evaluated the intestinal passage in pediatric patients treated with peritoneal dialysis by a lactulose hydrogen breath test and did not find any indications for delayed gastric emptying or pathological gastroesophageal reflux. The development of the ^{13}C octanoic acid breath test might be very useful to enlarge our limited understanding of the cause of these gastrointestinal symptoms in children with end stage renal disease.

In chapter 6 positive results are presented using urokinase as fibrinolytic agent in the case of fibrin obstruction of a peritoneal dialysis catheter in pediatric patients. As a conse-

quence of intraperitoneal hypercoagulation and relative hypofibrinolysis during PD, fibrin obstruction is one of the major causes of catheter malfunctioning in pediatric PD (38). Especially in catheter obstructions occurring more than 14 days after catheter implantation and in obstructions following peritonitis urokinase should always be administered. In early obstructions and in children without peritonitis, obstructions are mostly due to other causes, like catheter malpositioning and omentum wrapping which demand surgical intervention. Nevertheless an attempt with intraluminal fibrinolytic therapy should always be made. Unfortunately the future availability of urokinase on the market is uncertain. This demands new experiences with an alternative fibrinolytic agent. Tissue plasminogen activator (tPA) has a mechanism of action similar to that of urokinase and is a useful alternative for local fibrinolytic therapy in pediatric PD. Some good results with the use of tPA in adult patients have been presented (39, 40) and future studies will establish the effect of tPA also in children.

Another complication related to the peritoneal dialysis catheter is periluminal leakage of dialysis fluid. Leakage of dialysis fluids can complicate the effectiveness of dialysis and increases the risk of infections at the exit site, catheter tunnel and peritoneal membrane. Treatments for catheter leakage generally include decreasing of dialyate volumes, temporary rest from dialysis and surgical repair. Especially in acute peritoneal dialyis these treatment options cause an unacceptable delay in dialysis. The application of fibrin glue in the external part of the catheter tunnel has proven to be an effective treatment of periluminal catheter leakage, preventing the need of catheter replacement or other time-consuming treatments (chapter 7). Recently this has been confirmed by another group (41). Besides its use in acute peritoneal dialysis, the use of fibrin glue also deserves a major role in treatment of peritoneal dialysis catheter leakage in chronic peritoneal dialysis.

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Part VI

Summary
Samenvatting
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Summary

Peritoneal dialysis is the preferred modality for renal replacement therapy in children with chronic renal insufficiency. In the present thesis several clinical studies performed in children treated with peritoneal dialysis have been described. Transperitoneal transport was a major issue. Little has been published concerning the use of 7.5% icodextrin in children. Fluid kinetics with this glucose polymer based dialysis fluid were studied and compared with results in adult patients. The effect of two different dialysis fluids on intraperitoneal pressure was determined. The transport of drugs from the peritoneal cavity to the blood was the starting-point for assessment of the effectiveness of intraperitoneal administration of erythropoietin and antibiotics. An attempt was made to get more insight into gastroenterological complications of peritoneal dialysis and experiences are described with the use of urokinase in dialysis catheter obstruction and the use of fibrin glue in dialysis catheter leakage

An overview of our current knowledge on peritoneal dialysis in children has been presented in the **General Introduction**. A review is given of the peritoneal anatomy and its characterization with respect to transperitoneal transport. Peritoneal transport of fluid and solutes is discussed and a mathematical model for transperitoneal transport is introduced. Methods to evaluate peritoneal transport characteristics were introduced and discussed with respect to their application in patient care. Factors influencing peritoneal permeability were explained and several mediators involved in changes in peritoneal permeability were discussed. Developments in peritoneal dialysis solutions were discussed and special attention was paid to experiences with a glucose polymer based dialysis solution. The rationale for intraperitoneal administration of drugs was explained and experiences with intraperitoneal administration of erythropoietin and antibiotics were discussed

In **Chapter 1** the peritoneal equilibration test (PET) was applied to study the peritoneal transport characteristics using 7.5% icodextrin and 3.86% glucose. Additionally a comparison was made with peritoneal transport characteristics in adults. Solute transport and fluid kinetics in children were similar for 7.5% icodextrin and 3.86% glucose, except for transcapillary ultrafiltration (TCUF). This was explained by the slow ultrafiltration rate of 7.5% icodextrin. Peritoneal transport characteristics for the glucose solution were similar for children and adults, but for 7.5% icodextrin differences were found in TCUF and marker clearance, which equals the disappearance of fluid from the peritoneal cavity. Comparison of transport parameters and peritoneal characteristics reveals that there seem to be differences between the peritoneal transport pathways in children and adults. The absolute water flow through the aquaporins is similar in children and adults, which implies that the clinical efficacy of these water channels is similar. However further studies are needed to explore the differences in the amount and the functionality of the different peritoneal transport pathways and the consequences of these differences for the use of different osmotic agents.

In **Chapter 2** normal values for intraperitoneal pressure (IPP) in children were established and the effect of 3.86% glucose and 7.5% icodextrin on IPP during a 4-hour dwell were studied. IPP values were in the same range as those previously obtained in smaller patient groups. During a 4-hour dwell with 3.86% glucose a significant relation was found between IPP and TCUF. This result was likely mediated by an important increase of the intraperitoneal volume (IPV). During a dwell with 7.5% icodextrin no such relation was seen, which was explained by the small increase in IPV. Smaller children (children with a small BSA) have a more pronounced rise in IPP due to an increase of the IPV as compared to children with a larger BSA. It was concluded that the different effect of a colloid and a crystalloid osmotic agent on the change in IPP is due to the differences in fluid kinetics of these osmotic agents.

In **Chapter 3** the intraperitoneal administration of recombinant human erythropoietin has been addressed. Erythropoietin was injected in small bags, containing 50 mL NaCl 0.9% solution. The solution was instilled after complete drainage of the abdomen for a 10- to 12-hour dwell during the day. It was demonstrated that intraperitoneal administration of erythropoietin leads to an effective treatment of renal anemia. Maintenance dosages needed were similar to those when using the subcutaneous administration route. Our findings suggest that intraperitoneal erythropoietin should replace the subcutaneous administration, especially when adequate dialysis dose is obtained with a nightly dialysis regimen.

In **Chapter 4** the effectiveness of the combination of cefazolin and ceftazidime in the initial treatment of peritoneal dialysis-associated peritonitis episodes was evaluated. When peritonitis was diagnosed continuous antibiotic therapy was started, and depending on the causative microorganism therapy was adjusted. In 1 out of 50 episodes cefazolin and ceftazidime had to be replaced by another antibiotic medication. In all cases cloudiness of peritoneal fluid and clinical symptoms improved within 3 days after initiation of antibiotic therapy. In 90% of the peritonitis episodes no relapse occurred after ending therapy. Therefore this combination of a first- and a third-generation cephalosporin is effective in the treatment of peritoneal dialysis-associated peritonitis. Nephrotoxic and ototoxic side effects of aminoglycosides are avoided using this combination.

In **Chapter 5** the mechanisms underlying feeding disturbances in children treated with peritoneal dialysis were studied. The possible existence of a pathological reflux was examined and the intestinal passage was quantified by measuring the mouth-to-caecum transit time. Gastrointestinal motor function was not disturbed, which was in contrast with results obtained in studies performed by others. The presence of dialysis fluid did not have a negative effect on gastrointestinal motor function. Therefore we were not able to show a causative relation between gastrointestinal function and feeding disturbances.

In **Chapter 6** the effectiveness of fibrinolytic treatment with urokinase in children with peritoneal dialysis catheter obstruction was evaluated. Urokinase enhances degradation of fibrin which may dissolve an obstructing fibrin clot. In case of catheter obstruction 15000 IU of urokinase was injected into the catheter. An excellent effect of urokinase therapy

was seen in obstructions associated with peritonitis and in those obstructions occurring more than 14 days after catheter implantation. In obstructions occurring within 14 days after catheter implantation and in children without peritonitis, obstructions were more often caused by mechanisms unlikely to respond to urokinase. Because of the noninvasive character of intraluminal urokinase therapy, an attempt with urokinase should always be made, before surgery is considered.

Another peritoneal dialysis catheter related complication is periluminal leakage of dialysis fluid. In **Chapter** 7 a noninvasive therapy for catheter leakage was evaluated in children with acute peritoneal dialysis. Fibrin glue, a mixture of solubilized fibrinogen and thrombin, was applied in the external part of the catheter tunnel in children presenting with catheter leakage within the first 24 to 48 hours after catheter insertion. No relapse of dialysate leakage was seen after application of fibrin glue, and no infections occurred. Fibrin glue is a successful, simple and safe substance for the treatment of periluminal dialysis leakage in acute peritoneal dialysis, and surgical intervention is avoided. Therefore, it deserves a major role in the treatment of peritoneal dialysis catheter leakage in peritoneal dialysis patients of all ages.

Samenvatting

Peritoneaal dialyse is de meest aangewezen methode voor nierfunctie vervangende therapie voor kinderen met een chronische nierinsufficiëntie. In dit proefschrift worden klinische studies beschreven, die uitgevoerd werden bij kinderen die behandeld worden met peritoneaal dialyse. Transperitoneaal transport was daarbij een belangrijk onderwerp. Tot nu toe is er weinig gepubliceerd over het gebruik van icodextrine op de kinderleeftijd. De vloeistofkinetiek van deze dialysevloeistof -die gebaseerd is op glucosepolymeren- werd bestudeerd en vergeleken met resultaten die eerder waren verkregen bij volwassenen. Tevens werd het effect van twee verschillende dialysevloeistoffen op de intraperitoneale druk werd bekeken. Het transport van medicijnen van de peritoneaal holte naar het bloed vormde het uitgangspunt voor studies naar de effectiviteit van de intraperitoneale toediening van antibiotica en erythropoiëtine. Een poging werd gedaan om meer inzicht te krijgen in de gastroenterologische complicaties die gepaard gaan met peritoneaal dialyse. Voorts werd een beschrijving gegeven van de ervaringen die werden opgedaan met het gebruik van urokinase in het geval van obstructie van peritoneaal dialysecatheters, en het gebruik van weefsellijm in het geval van lekkage langs peritoneaal dialysecatheters.

In de **Algemene Inleiding** wordt een overzicht gegeven van de huidige kennis op het gebied van peritoneaal dialyse op de kinderleeftijd. De hoofdlijnen van de peritoneale anatomie worden beschreven en de karakterisering van de peritoneaal membraan met betrekking tot het transperitoneale transport. Het peritoneale transport van vloeistof en vaste deeltjes wordt besproken en het meest gebruikte wiskundige model voor transperitoneaal transport wordt uitgelegd. Verschillende methodes voor het evalueren van peritoneale transportkarakteristieken worden uitgelegd en bekeken in relatie tot de zorg voor de patiënt. Factoren die van invloed zijn op de permeabiliteit van de peritoneaal membraan worden uitgelegd en verscheidene mediatoren die betrokken zijn bij veranderingen in de permeabiliteit van de peritoneaal membraan worden besproken.

Ontwikkelingen in peritoneaal dialysevloeistoffen worden besproken en extra aandacht wordt besteed aan de ervaringen die zijn opgedaan met het gebruik van dialysevloeistof gebaseerd op glucosepolymeren. De basis voor de intraperitoneale toediening van medicijnen wordt uitgelegd en eerder gepubliceerde ervaringen met het intraperitoneale toediening van erythropoiëtine worden weergegeven.

In **Hoofdstuk 1** wordt de peritoneaal equilibratie test (PET) toegepast voor de bestudering van peritoneale transportkarakteristieken tijdens het gebruik van icodextrine en 3,86% glucose. Aansluitend wordt er een vergelijking gemaakt met peritoneale transportkarakteristieken bij volwassenen. Het transport van vaste deeltjes en de vloeistofkinetiek bij kinderen waren vergelijkbaar voor icodextrine en 3,86% glucose, behalve voor de transcapillaire ultrafiltratie (TCUF). Dit laatste wordt verklaard door de langzame, gestage ultrafiltratie die icodextrine te weeg brengt. De peritoneale transportkarakteristieken voor de glucosevloeistof waren vergelijkbaar voor kinderen en volwassenen, maar voor de icodextrinevloeistof werden er verschillen gevonden in de TCUF en de klaring van de marker, die gebruikt wordt

als maat voor verdwijning van vloeistof uit de peritoneaal holte. Berekeningen lieten zien dat de hoeveelheid en de effectiviteit van de aquaporines bij de volwassenen lager lag dan bij de kinderen. De veronderstelling is dat dit verschil verklaard wordt door een verschil in blootstelling aan glucose en/of een verschil in behandelingsduur. Er is daarom reden om aan te nemen dat icodextrine goed toepasbaar is op de kinderleeftijd, maar verdere studies zullen nodig zijn om de onderliggende oorzaak voor het verschil in vloeistofkinetiek te doorgronden.

In **Hoofdstuk 2** worden normaalwaarden vastgesteld voor de intraperitoneale druk op de kinderleeftijd, en het effect van 3,86% glucose en icodextrine op de intraperitoneale druk wordt bestudeerd. De waardes die gevonden werden voor de intraperitoneale druk bevonden zich in dezelfde range als de gepubliceerde waardes, die verkregen waren in kleinere studie groepen. Gedurende een verblijfsperiode van 4 uur met 3,86% glucose veranderde de intraperitoneale druk significant in relatie tot de TCUF. Dit was waarschijnlijk een gevolg van de toename in het intraperitoneale volume. Gedurende een zelfde verblijfsperiode met icodextrine werd een dergelijke relatie niet gevonden. Dit kan worden verklaard door de geringe toename van het intraperitoneale volume. Bij kleinere kinderen is er een meer uitgesproken stijging van de intraperitoneale druk ten gevolge van een stijging van het intraperitoneale volume, dan het geval is bij kinderen met een groter lichaamsoppervlakte. Dit effect werd alleen waargenomen tijdens de verblijfsperiode met 3,86% glucose. Daarom is het waarschijnlijk, dat de verschillen die gezien worden tijdens verblijfsperiodes met verschillende dialysevloeistoffen, een gevolg zijn van de verschillen in vloeistofkinetiek van de betreffende dialysevloeistoffen.

In **Hoofdstuk 3** wordt de intraperitoneale toediening van recombinant humaan erythropoiëtine beschreven. Erythropoiëtine werd geïnjecteerd in kleine zakjes met daarin 50 ml NaCl 0,9%-oplossing. Na een complete drainage van de buik, liet men de oplossing inlopen, waarna deze overdag gedurende 10 tot 12 uur achterbleef in de peritoneaal holte. Er werd aangetoond dat intraperitoneale toediening van erythropoiëtine leidt tot een effectieve behandeling van renale anemie. De benodigde onderhoudsdoseringen waren gelijk aan de onderhoudsdoseringen die nodig zijn bij gebruik van de subcutane toedieningsweg. Onze bevindingen suggereren dat de subcutane toediening van erythropoiëtine dient te worden vervangen door intraperitoneale toediening, met name als er met nachtelijke intermitterende dialyse een adequate dialysedosis wordt verkregen.

In **Hoofdstuk 4** wordt de effectiviteit van de combinatie cefazoline en ceftazidim voor de initiële behandeling van peritoneaal dialyse-geassocieerde peritonitis geëvalueerd. Zodra peritonitis was gediagnostiseerd werd gestart met continue behandeling met antibiotica. Afhankelijk van de sensitiviteit van het micro-organisme werd de behandeling vervolgens aangepast. In één van de 50 peritonitis episodes was het nodig om cefazoline en ceftazidim te vervangen door een ander antibioticum. In alle gevallen verbeterden de troebelheid van het dialysaat en de klinische symptomen binnen drie dagen na het starten van de antibiotica. In 90% van de gevallen trad er geen recidief op na het beëindigen van de behandeling. Er is daarom reden om aan te nemen dat deze combinatie van een eerste- en een derde-gene-

ratie cephalosporine effectief is voor de behandeling van peritoneaal dialyse-geassocieerde peritonitis. De nefrotoxische en ototoxische bijwerkingen van aminoglycosides, die vaak in andere schema's worden gebruikt, worden vermeden bij het gebruik van deze combinatie van antibiotica.

In **Hoofdstuk 5** worden de mechanismen bestudeerd die ten grondslag liggen aan de voedingsstoornissen, die gezien worden bij kinderen die behandeld worden met peritoneaal dialyse. Het mogelijke bestaan van een pathologische reflux werd onderzocht en de snelheid van de maag-darmpassage werd gekwantificeerd door meting van de doorgangstijd van mond tot coecum. De motorische functie van het maagdarmkanaal bleek niet gestoord te zijn, dit in contrast tot de resultaten die verkregen zijn met eerder gepubliceerde studies. Daarnaast had de aanwezigheid van dialysaat in de peritoneaal holte geen negatieve invloed op de motorische functie van het maagdarmkanaal. Daarom was het niet mogelijk om een oorzakelijk verband tussen de functie van het maagdarmkanaal en de voedingsstoornissen aan te tonen.

In **Hoofdstuk 6** werd de behandeling van obstructie van de peritoneaal dialysecatheter met intraluminaal toegediend urokinase geëvalueerd. Urokinase versnelt de degradatie van fibrine, hetgeen mogelijk kan leiden tot het oplossen van een obstruerende fibrine prop. In het geval van obstructie van een catheter werd 15000 IE urokinase in de catheter geïnjecteerd. Er werd een uitstekend resultaat waargenomen van de behandeling met urokinase in die gevallen van obstructie die gerelateerd waren aan een peritonitis episode, en bij obstructies die meer dan 2 weken na plaatsing van de catheter optraden. Bij de obstructies die binnen 14 dagen na het plaatsen van de catheter optraden en bij kinderen die geen peritonitis hadden, werden de obstructies grotendeels veroorzaakt door mechanismen die niet reageerden op behandeling met urokinase, zoals verstopping met omentum. Vanwege het niet-invasieve karakter van de intraluminale behandeling met urokinase, lijkt het daarom geïndiceerd om altijd hiermee een poging te wagen, voordat chirurgisch ingrijpen wordt overwogen.

Een andere belangrijke complicatie van peritoneaal dialyse is de lekkage van dialysevloeistof uit de cathetertunnel. In **Hoofdstuk** 7 wordt een evaluatie gegeven van de niet-invasieve behandeling van catheterlekkage bij kinderen die behandeld worden met acute peritoneaal dialyse. Weefsellijm -een mengsel van fibrinogeen- en thrombine-oplossingen- werd toegediend in het externe gedeelte van de cathetertunnel bij kinderen die zich gedurende de eerste 24 tot 48 uur na plaatsing van de catheter presenteerden met lekkage. In geen van de gevallen zagen we een recidief van de lekkage en/of het optreden van infecties. Weefsellijm lijkt een succesvolle, eenvoudige en veilige substantie voor de behandeling van lekkage van dialysevloeistof bij peritoneaal dialyse. Hierdoor is chirurgische interventie overbodig. Daarom wordt geconcludeerd dat weefsellijm een belangrijke plaats verdient bij de behandeling van lekkage van de peritoneaal dialysecatheter bij patiënten van alle leeftijden.

Samenvatting voor de (nog) niet ingewijden

Als er sprake is van een verminderde nierfunctie, dan is het lichaam niet voldoende in staat om afvalstoffen en overtollig water uit te scheiden. Het hebben van een slechte nierfunctie op de kinderleeftijd heeft ernstige gevolgen, zoals het optreden van botontkalking, groeistoornissen, aderverkalking en beschadiging van de hersenen. Uiteindelijk kunnen kinderen ook overlijden aan de gevolgen van hun slechte nierfunctie. Om deze ernstige gevolgen te voorkomen bestaan er mogelijkheden om de nierfunctie te vervangen. De meest ideale manier om de nierfunctie te vervangen is de uitvoering van een niertransplantatie, waarbij de patiënt een nier krijgt van een familielid of van een overledene. Door het beperkte aantal donornieren dat beschikbaar is, zijn de wachtlijsten hiervoor echter lang. Naast de niertransplantatie zijn er ook andere technieken beschikbaar om de nierfunctie te vervangen: bloedspoeling en buikspoeling.

Bij bloedspoeling, of hemodialyse, vindt de zuivering van het bloed direct plaats via de bloedbaan. Bij buikspoeling, ook wel peritoneaal dialyse genoemd, worden de afvalstoffen in het bloed en het overtollige water via het buikvlies aan het lichaam onttrokken. Hiertoe wordt er een dialysevloeistof via een verblijfscatheter (een catheter die permanent door de buikwand heen gaat) in de buikholte gebracht. De dialyse vloeistof heeft bepaalde eigenschappen waardoor de afvalstoffen en het overtollige water via de bloedvaatjes in het buikvlies naar de dialyse vloeistof diffunderen (het natuurkundige proces waarbij ongelijke vloeistoffen vermengen). Door na een bepaalde tijd de dialyse vloeistof weer uit de buik te laten lopen en er vervolgens weer nieuwe dialyse vloeistof in te laten lopen, wordt het bloed gezuiverd en het overtollige water afgevoerd en zo vervang je dus de functie van de nieren. Naast de dialyse is het belangrijk dat kinderen zich aan een dieet houden en dat ze een beperkte hoeveelheid vocht innemen.

Peritoneaal dialyse is de meest gebruikte behandeling voor het vervangen van de nierfunctie op de kinderleeftijd. In het merendeel van de gevallen worden de kinderen 's nachts, tijdens hun slaap, gedialyseerd. Een machine zorgt er voor dat de dialyse vloeistof in de buik loopt en er later weer uitloopt. Dit heeft een aantal voordelen ten opzichte van hemodialyse. Zo kan peritoneaal dialyse thuis worden gedaan, zodat kinderen gewoon overdag naar school kunnen, terwijl kinderen voor hemodialyse vaak 3 keer per week naar het ziekenhuis moeten komen. Door de aanwezigheid van de verblijfscatheter in de buikwand hoeven de kinderen niet elke keer geprikt te worden. En verder hebben kinderen die behandeld worden met peritoneaal dialyse vaak meer vrijheid in hun dieet en hun vochtinname dan kinderen die behandeld worden met hemaodialyse. Ondanks de voordelen blijft het echter een feit dat peritoneaal dialyse een zware belasting vormt voor zowel de ouders als het kind.

In dit proefschrift worden een aantal studies beschreven, die uitgevoerd zijn bij kinderen die behandeld worden met peritoneaal dialyse. Een belangrijk uitgangspunt voor het merendeel van die studies was het transport van deeltjes en vloeistof over het buikvlies. Er wordt aangenomen dat er een drietal verschillende soorten (hele kleine) gaatjes in het buikvlies zitten, die bepalend zijn voor de mate waarin deeltjes over het buikvlies kun-

nen diffunderen. Door de grootste gaatjes kunnen macromoleculen zoals eiwitten, door de kleine gaatjes kunnen kleine deeltjes zoals ureum en glucose, en door de ultra kleine gaatjes kan alleen water diffunderen. Door die gaatjes vindt dus transport plaats van het bloed naar de buikholte, maar tevens vindt er transport plaats van vloeistof en deeltjes van de buikholte naar het bloed.

In het eerste deel van dit proefschrift worden de effecten bestudeerd van icodextrine. Icodextrine is een dialysevloeistof die zich onderscheidt van andere dialyse vloeistoffen omdat er geen glucose in zit. Hoewel glucose heel goed in staat is om afvalstoffen en overtollig vocht aan de bloedbaan te onttrekken, zorgt het tegelijk voor een beschadiging van het buikvlies. Met behulp van een gestandaardiseerde test (de peritoneaal equilibratie test, kortweg PET) is er gekeken naar de effecten van icodextrine op het transport van deeltjes en vloeistof over het buikvlies. Tevens is er gekeken of het gebruik van icodextrine effect had op de druk die ontstaat in de buikholte (IPP). We zagen dat de effecten van icodextrine op het transport over het buikvlies vergelijkbaar zijn met de effecten die beschreven zijn bij volwassen patiënten. Onze resultaten duiden er op, dat het transport over het buikvlies niet exact hetzelfde lijkt te verlopen bij kinderen en volwassenen. Toch is het uiteindelijke effect van icodextrine wel hetzelfde. Verdere studies zullen nodig zijn om de verschillen in transport beter te bestuderen, om ze goed te kunnen verklaren. De druk in de buikholte liep niet zo snel op tijdens het gebruik van icodextrine, als tijdens het gebruik van een glucose houdende vloeistof. Dit konden we verklaren door het feit dat er relatief weinig water aan de bloedbaan werd onttrokken tijdens het gebruik van icodextrine, waardoor het volume in de buikholte ook minder toenam.

In het tweede deel van dit proefschrift worden ervaringen besproken, die opgedaan zijn met de toediening van medicijnen via de verblijfscatheter. We hebben gekeken naar de effectiviteit van een combinatie van antibiotica voor de behandeling van buikvliesontsteking. Buikvliesontsteking is een vervelende complicatie van peritoneaal dialyse. De gebruikte combinatie van antibiotica heeft als voordeel dat ernstige bijwerkingen, zoals doofheid of een verdere achteruitgang van de nierfunctie niet optreden. Uit onze resultaten blijkt dat de combinatie van antibiotica goed geschikt is voor de behandeling van buikvliesontsteking. Voor de toediening van een aantal medicijnen is het nodig om meerdere keren per week een prik te geven. Dit vormt vaak een zware belasting voor zowel het kind als de ouders. We hebben onderzocht of het mogelijk is om bloedarmoede goed te behandelen door erythropoiëtine via de verblijfscatheter in de buikholte te spuiten in plaats van toediening via de gebruikelijke prikjes onder de huid. We zagen dat de behandeling van de bloedarmoede net zo goed verliep en dat er ook niet meer van het medicijn nodig was dan voorheen.

In het derde deel worden studies besproken die betrekking hebben op enkele veel voorkomende complicaties van peritoneaal dialyse. Zo hebben veel kinderen die behandeld worden met peritoneaal dialyse last van misselijkheid en een gebrek aan eetlust. We hebben gekeken of er afwijkingen zijn in de functie van de maag en de darmen, die de oorzaak kunnen zijn voor deze voedingsproblemen, maar we hebben geen aanwijzingen gevonden dat dat ook zo is.

Een andere complicatie van peritoneaal dialyse is het verstopt zitten van de verblijfscatheter. Dit heeft als gevolg dat er niet gedialyseerd kan worden. We zagen dat in veel gevallen voorkomen kan worden dat er geopereerd moet worden om een nieuwe catheter te plaatsen, door de verstopping in de catheter te behandelen met urokinase. Verder bleek, dat lekkage van een verblijfscatheter behandeld kan worden met het aanbrengen van weefsellijm op de plaats van de lekkage. Ook deze relatief eenvoudige en niet-belastende behandeling kan voorkomen dat het nodig is om een chirurg te vragen om een catheter te verwisselen.

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Curriculum vitae

Esther Rusthoven werd geboren op 31 augustus 1974 te Delfzijl. In 1992 behaalde zij haar VWO diploma aan O.S Huygenwaard te Heerhugowaard. Vanaf 1992 volgde zij de studie Geneeskunde aan de Faculteit der Medische Wetenschappen van de Rijksuniversiteit Groningen, alwaar zij in 1997 haar propadeuse behaalde. In 1996 verrichtte zij enkele maanden onderzoek op de afdeling Metabole Stoornissen in het Hopital Necker des Enfants Malades te Parijs (hoofd Prof. dr. J.M. Saudubray). Het doctoraal examen Geneeskunde behaalde zij in 1997, gevolgd door het artsexamen in 1999. Van 1999 tot 2002 was zij werkzaam als arts-onderzoeker op de afdeling kindernefrologie van het Wihelmina Kinderziekenhuis te Utrecht (hoofd afdeling prof. dr. C.H. Schröder). In 2002 begon zij aan de opleiding tot kinderarts in het VU Medisch Centrum te Amsterdam (opleider prof. dr. J.J. Roord) en het Deventer Ziekenhuis te Deventer (opleider dr. C.A. Ultee). Zij besloot met deze opleiding te stoppen in 2004. Sinds augustus 2004 is zij werkzaam als consultatiebureau-arts bij Thuiszorgorganisatie Amstelring Plus te Amstelveen.

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