

The kinetics of water transperitoneal transport during long-term peritoneal dialysis performed using icodextrin dialysis fluid

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KEY WORDS

icodextrin, peritoneal dialysis, peritoneal transport

ABSTRACT

INTRODUCTION Dialysis fluid containing icodextrin is used in patients on peritoneal dialysis (PD) because of its significant ultrafiltration properties. The use of the fluid in treating patients with congestive heart failure resistant to diuretics has also been reported.

OBJECTIVES The aim of the study was to evaluate water peritoneal transport during a 16-hour dialysis exchange performed using icodextrin-containing dialysis fluid.

PATIENTS AND METHODS Eleven clinically stable patients were enrolled in the study (5 women and 6 men; mean age, 50.4 ± 18.3 years), treated with PD for 26.9 ± 22.4 months. Water transperitoneal transport was evaluated using a modified version of Babb-Randerson-Farrell thermodynamic model of membrane transport with human albumin marked with iodine as the marker of intraperitoneal volume. Based on blood and dialysate samples collected during the 16-hour dialysis exchange, the intraperitoneal volume of dialysate and dialysate reverse absorption were calculated.

RESULTS There were no clinical complications associated with the use of icodextrin fluid during the study. A significant increase in intraperitoneal volume of dialysate (950 ml on average) compared to the initial value was observed in the whole group at the 16th hour of the exchange.

CONCLUSIONS The study demonstrated that dialysis fluid with icodextrin ensured effective ultrafiltration during a 16-hour dialysis exchange. This indicates its potential usefulness in the treatment of patients with severe congestive heart failure with or without coexisting end-stage renal disease.

INTRODUCTION Our studies on peritoneal dialysis (PD), full of surprises and unexpected findings, began more than 40 years ago. At that time, Zofia Górko-Wańkowicz was trained in a newly introduced method of intermittent PD at the First Department of Internal Diseases of the Warsaw Medical Academy, which an associate professor, Tadeusz Orłowski was in charge of.¹ Until the end of the 1970s, the approach was used only in hospitalized patients. In November 1979, Zofia Wańkowicz was one of the first in Europe to apply continuous ambulatory PD (CAPD) at our center using the equipment designed by us. In subsequent years, we developed our own schedule of CAPD and the method of automatic PD (APD).

Since 1990s, we have conducted a number of studies both on PD adequacy and the kinetics of peritoneal transport of water and substances. The present paper presents our current scientific work.

Even in the 1990s, because of its continuous character PD was considered an effective method for treating overhydration in patients with end-stage renal disease subjected to extended dialysis therapy.² However, at the beginning of the 21st century, a number of papers were published, which indicated overhydration as a major clinical challenge in PD.³⁻⁵ Overhydration in PD is associated with excessive supply of salt and fluids, and low removal of water from the organism on the one hand, and with real ultrafiltration

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insufficiency of peritoneal membrane on the other. The latter is a less common cause of overhydration. Ultrafiltration insufficiency is diagnosed if the volume of ultrafiltrate does not exceed 400 ml per dialysis exchange, despite using hypertonic dialysis fluid with 3.86% glucose. Peritoneal ultrafiltration insufficiency may occur as a result of increased transport of small particles and increased lymphatic absorption, defects in intracellular water transportation following dysfunction of aquaporins or anatomic changes, including peritoneal membrane surface reduction in response to the process of progressive peritoneum sclerosis.^{6,7} According to Heimbürger et al., ultrafiltration insufficiency develops in 2.5% of patients within a year, in 9.5% of patients within 3 years, and in 31% of patients after 6 years of PD treatment.⁸ Ultrafiltration insufficiency of peritoneal membrane requires that 15% of patients on PD are transferred to the extended program of hemodialysis.⁹ Ultrafiltration in PD has been shown to correlate with patient and method survival.¹⁰⁻¹²

Standard dialysis fluids used in PD contain glucose, which removes water from the organism. Dialysis fluid, hypertonic to plasma, induces the flow of water from the vascular bed to the peritoneal cavity. In the course of peritoneal exchange, the osmotic gradient deteriorates because of glucose absorption from the peritoneal cavity to the vascular bed. Ultrafiltration process and overhydration are reduced in patients demonstrating high peritoneal transport, i.e. rapid glucose absorption from the dialysis fluid, which causes a sudden decline of the osmotic gradient. This may lead to clinical complications of overhydration.

In the early 1990s, an alternative dialysis fluid was introduced to PD which contained glucose polymer, i.e. icodextrin, as an osmotic agent.^{13,14} Icodextrin is derived by partial hydrolysis of maize starch. Its average molecular weight is 16 800 daltons, total osmolarity reaches 282 mOsm/l, and pH is 5.3. The dialysis fluid containing icodextrin has been used in long-term dialysis exchange in patients on CAPD and in long-term daily exchange in patients on APD. There is also data available in recent literature on the use of the fluid in the treatment of patients with refractory congestive heart failure with or without the coexisting end-stage renal disease.^{15,16}

The aim of the study was to evaluate water peritoneal transport during the 16-hour dialysis exchange conducted with the use of icodextrin dialysis fluid. We also considered the use of the fluid in patients with heart failure without coexisting end-stage renal disease. We used the thermodynamic model of membrane transport which allowed us to determine the intraperitoneal volume of dialysate at appropriate time points of the exchange.¹⁷⁻¹⁹

PATIENTS AND METHODS We recruited 11 subjects (5 women and 6 men; mean age of 50.4 ± 18.3

years), who had been on PD for 26.9 ± 22.4 months. In 8 patients renal diseases were caused by primary glomerulopathies, and in 3 patients by diabetic nephropathy. We recruited clinically stable patients, in whom the last episode of dialysis peritonitis occurred at least 3 months prior to the study. All patients gave informed consent to participate in the study.

Prior to the study, the patients received 1.0 g of vancomycin intravenously to reduce the risk of dialysis peritonitis. After the dialysate from the overnight exchange had been removed from the peritoneal cavity, the patients underwent a 16-hour exchange with icodextrin dialysis fluid: icodextrin 75 g/l, sodium 133 mmol/l, calcium 1.75 mmol/l, magnesium 0.25 mmol/l, chlorides 96 mmol/l, lactates 40 mmol/l, osmolarity 282 mOsm/kg and pH 5.3. The volume of the dialysis fluid introduced to the peritoneal cavity was 2 litres. An initial dose of 0.2 g of human albumin was introduced into the bag containing the dialysis fluid previously heated up to the temperature of 37°C in order to minimize the adhesion of marked albumin to the bag. Then the system was flushed using “flush before fill” technique and 10 mg of human serum albumin (HSA) marked with ¹²⁵J was introduced into the bag. After thorough mixing, the dialysis fluid was introduced into the peritoneal cavity. Then, the patient was disconnected from the system and a tee-joint was placed on the transfer-set. The volume of the fluid which was introduced into the peritoneal cavity was calculated by means of subtracting the bag’s dry mass from the weight of the bag containing the dialysis fluid. After thorough mixing, the dialysis fluid was introduced into the peritoneal cavity. In the 0, 3, 15, 30, 60, 90, 120, 180, 240, 480, 720 and 960 minute of the dialysis, 10 ml of dialysate was collected using the tee-joint. The syringe was previously flushed ten times with 15 ml of the fluid. Directly before collecting each sample, the patient was asked to make movements in order to help the fluid mix thoroughly in the peritoneal cavity. The radioactivity of isotope was assayed in the collected samples. Blood samples were collected in the 0, 15, 60, 120, 240, 480, 720 and 960 minute of the dialysis.

After 960 minutes of dialysis exchange, the dialysate was released from the peritoneal cavity and its volume was measured by subtracting the bag’s dry mass from the total weight of the bag containing the dialysate. Then, in order to assess the residual volume a 5-minute peritoneal exchange was carried out with Dianeal PD₁ dialysis fluid with 1.36% glucose and without the marked albumin. The volume of the fluid was estimated as described above. Then, the patient was disconnected from the system and the tee-joint was placed on the transfer-set. The patient moved about for 5 minutes and then 5 ml of dialysate was collected through the tee-joint (the syringe flushed as before) in order to assay the radioisotope activity. After 5 minutes, the dialysate was released from the peritoneal cavity and the procedure was completed.

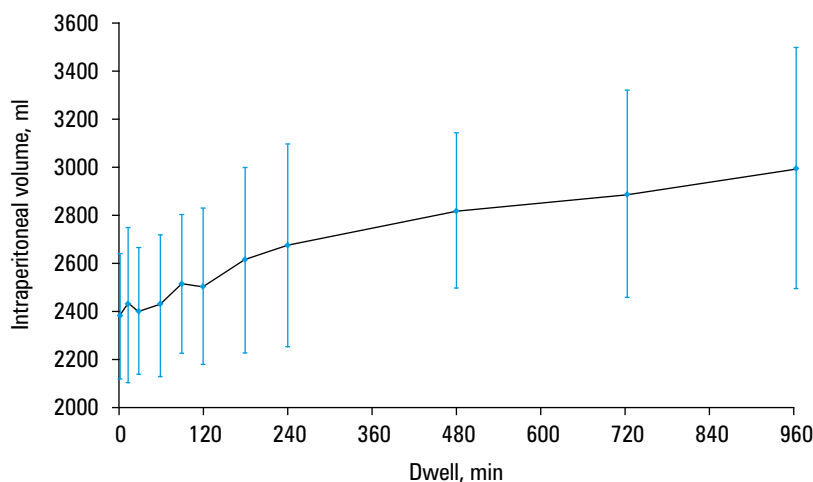


FIGURE Intraperitoneal dialysate volumes during 16-hour dwell with icodextrin solution

For evaluation of peritoneal kinetics, a modified version of Babb-Randerson-Farrell thermodynamic model of membrane transport¹⁷⁻¹⁹ with ¹²⁵J-HSA as the marker of intraperitoneal volume was used.

The dialysate intraperitoneal volume was calculated on the basis of human albumin marked with iodine dissolution taking into account the co-efficient of ¹²⁵J-HAS elimination (K_e , ml/min) from the peritoneal cavity and the volume of dialysate samples collected during the exchange. The radioactivity of dialysate and blood samples was measured using ZM 701 GM set with -1 probe of the POLON company. Biochemical tests were performed using Cobas Integra 760 autoanalyzer (Roche, Switzerland). The calculations were made using Microsoft Office Excel.

RESULTS We did not observe any clinical complications associated with the use of icodextrin fluid during the study or during several weeks of follow-up.

The **FIGURE** shows the curve of intraperitoneal dialysate volume (\pm standard deviation [SD] average) obtained during a 16-hour dialysis exchange performed with icodextrin solution. The curve is rising to the 960th minute. Absorption co-efficient (K_e) was 0.68 ± 0.38 ml/min. We observed a significant increase in dialysate intraperitoneal volume compared to the initial value, with a mean of 950 ml ($p = 0.002$). The increase was maintained until the end of the study. The minimum intraperitoneal volume was 2372 ml and the maximum was 3621 ml.

DISCUSSION The curve of intraperitoneal volume was of non-uniform character (**FIGURE**). After a sudden increase which occurred in the 3rd minute of the exchange, a decrease in intraperitoneal volume was observed, which lasted until the 60th minute of the exchange. Another decline occurred between the 90th and 120th minute. After 120 minutes of the exchange the curve of intraperitoneal volume started to increase.

In the available data, not very precise methods to evaluate ultrafiltration achieved with the use of icodextrin fluid have been used. These methods measured either the volume of dialysate released

from the peritoneal cavity or ultrafiltration as the difference between the volume of fluid introduced and restored from the peritoneal cavity. Ultrafiltration achieved by using icodextrin fluid was often compared with standard fluids with different glucose concentrations.

In 1992, the MIDAS (Multicentre Investigation of Icodextrin in Ambulatory Peritoneal Dialysis) trial with icodextrin dialysis fluid was conducted in Great Britain.²⁰ The study recruited >200 patients from 11 centers specializing in PD. Ultrafiltration was 527 ± 36 ml after 8 hours of dialysis with icodextrin fluid, and 561 ± 44 ml after 12 hours, which was 5.5 times greater compared to the results produced by the fluid with 1.36% concentration of glucose.

The study conducted with the use of icodextrin in patients on APD showed that average ultrafiltration during a 14–15-hour dialysis exchange ranged 200–500 ml. Woodrow et al. applied icodextrin fluid in 17 patients on APD. Average time of dialysis exchange was 15 hours and average ultrafiltration was 260 ml.²¹ Posthuma et al. conducted a randomized, open, prospective trial with 38 patients on continuous cyclic PD (CCPD). During the daily, 14–16-hour dialysis exchange, icodextrin dialysis fluid was applied in 19 patients; other patients used glucose fluid with concentrations adjusted to their individual needs. In the first group a significant increase in ultrafiltration was observed during the daily exchange, 200 ml on average, compared to initial values ($p < 0.001$). The tendency was maintained for 2 years of PD schedule. Daily ultrafiltration also increased, although the rise was not statistically significant compared to total ultrafiltration measured at the beginning of the study.²² Neri et al. evaluated ultrafiltration in 10 patients on CAPD and in 10 patients on APD. In the 1st group the dialysis exchange with icodextrin fluid lasted for 11.5 ± 1.8 hours; ultrafiltration was 631 ± 253 ml. In the 2nd group the exchange lasted for 14.8 ± 0.5 hours, a substantially lower ultrafiltration rate was observed, i.e. 234 ± 215 ml ($p < 0.001$).²³ In a prospective study Jeloka et al. used icodextrin dialysis fluid in 36 patients on APD. They did not observe any differences in ultrafiltration rate in the course of a 14-hour dialysis exchange. After 10 hours ultrafiltration was 351.73 ± 250.59 ml, and after 14 hours it was 371 ± 258.25 ml ($p = 0.83$). A significant difference was observed only in patients with high intraperitoneal transport. In these patients ultrafiltration was higher compared to patients being slow transporters ($p < 0.04$).²⁴ All tests were performed with no use of mathematic intraperitoneal transport models.

Unlike the authors described above, Ho-Dac-Pannekeet et al. evaluated PD kinetics with icodextrin dialysis fluid using thermodynamic model of membrane transport in which dextran 70 was the intraperitoneal volume marker.²⁵ The method is determined as the test of standard analysis of peritoneum permeability.²⁶ The study

conducted during a 9-hour dialysis exchange showed that transcapillary ultrafiltration rate (TCUFR) and effective lymphatic absorption were comparable for icodextrin and glucose fluids with 3.86% glucose concentration.²⁵ However, the curves of the fluid volume in the peritoneal cavity dependencies (proportional to ultrafiltration) in relation to time differed between the two types of fluid. For the fluid containing 3.86% glucose, the curve is hyperbolic in shape and TCUFR drop in time is associated with glucose absorption from the peritoneal cavity to blood and a decline of osmolar gradient as the driving force of ultrafiltration. For icodextrin, the curve is of linear shape, which allows to expect higher ultrafiltration net with the extended duration of dialysis exchange. That was the result we obtained in our study.

There have been reports on the use of peritoneal ultrafiltration in patients with heart failure resistant to conventional treatment and with or without coexisting renal disease published in the literature on PD for the past 10 years.²⁷⁻²⁹ It has been demonstrated that both CAPD and APD improve the quality of life, reduce the need for diuretics, and are associated with less frequent and shorter hospital stays in patients with congestive heart failure. Gotloib et al. showed that APD method produces a beneficial hemodynamic effect on the heart and kidneys for continuous and hemodynamically safe ultrafiltration.²⁹ Bertoli et al. described the case of 2 patients with severe congestive heart failure (New York Heart Association [NYHA] class III and IV) without the coexisting end-stage renal disease, who underwent overnight dialysis exchange with icodextrin fluid. During 1-year observation, heart ejection fraction in both patients improved from 25% to 50% and from 22% to 27%, respectively. None of them required hospitalization and their quality of life improved.¹⁵ Basil et al. described 4 patients with congestive heart failure (IV class of NYHA) and different glomerular filtration rates (GFR).¹⁶ 3 patients underwent 1 overnight exchange with icodextrin dialysis fluid; 1 patient underwent exchange with icodextrin fluid and 1 exchange with standard fluid of 1.36% glucose. Average follow-up period was 24.3 ± 15.6 months (from 13 to 43 months). In all patients a statistically significant increase in diuresis (from 587.5 ± 165.2 to 1700.0 ± 141.4 ml, $p < 0.003$), statistically non-significant decrease in creatinine serum levels (from 3.55 ± 1.12 to 2.37 ± 0.35 mg/dl), and a statistically significant decrease in body weight (from 80.3 ± 7.0 to 69.0 ± 5.1 kg, $p < 0.007$) were observed. In all patients cardiac function improved, which was evidenced by a change in NYHA class (from 4.0 ± 0.0 to 2.5 ± 2.6, $p < 0.01$). There was also shorter hospital stay (from 4.4 ± 2.0 to 0.7 ± 1.5 days/month, $p < 0.04$).

SUMMARY The study, in which a precise method of dialysate intraperitoneal volume determination was used, showed that icodextrin dialysis fluid

ensured effective ultrafiltration during a 16-hour dialysis exchange. This indicated its usefulness in the treatment of patients with severe congestive heart failure without coexisting end-stage renal disease (GFR > 15 ml/min).

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Kinetyka transportu przezotrzewnowego wody podczas długotrwałej dializy otrzewnowej prowadzonej z zastosowaniem płynu dializacyjnego zawierającego ikodekstrynę

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SŁOWA KLUCZOWE

dializa otrzewnowa,
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transport
otrzewnowy

STRESZCZENIE

WPROWADZENIE Płyn dializacyjny zawierający ikodekstrynę – z uwagi na swoje znaczące właściwości ultrafiltracyjne – znalazł zastosowanie u pacjentów leczonych dializą otrzewnową, jak również pojawiły się doniesienia na temat stosowania tego płynu w leczeniu pacjentów z zastoinową niewydolnością serca oporną na diuretyki.

CELE Celem pracy była ocena transportu otrzewnowego wody podczas 16-godzinnej wymiany dializacyjnej prowadzonej z zastosowaniem płynu dializacyjnego zawierającego ikodekstrynę.

PACJENCI I METODY W badaniu uczestniczyło 11 stabilnych klinicznie pacjentów (5 kobiet i 6 mężczyzn; średnia wieku $50,4 \pm 18,3$ roku) leczonych dializą otrzewnową przez okres $26,9 \pm 22,4$ miesiąca. W ocenie transportu przezotrzewnowego wody posłużono się zmodyfikowanym termodynamicznym modelem transportu membranowego Babb-Randerson-Farrell'a z zastosowaniem jako znacznika objętości wewnątrzotrzewnowej albuminy ludzkiej znakowanej jodem. Na podstawie pobranych podczas 16-godzinnej wymiany dializacyjnej próbek krwi i dializatu obliczono objętość wewnątrzotrzewnową dializatu oraz absorpcję zwrotną dializatu.

WYNIKI Podczas badania nie odnotowano klinicznych powikłań wynikających ze stosowania płynu z ikodekstryną. W całej badanej grupie, w 16. godzinie wymiany stwierdzono znamienny wzrost objętości wewnątrzotrzewnowej dializatu średnio o 950 ml w porównaniu do wartości wyjściowej.

WNIOSKI Przeprowadzone badania wykazały, że płyn dializacyjny z ikodekstryną zapewnia efektywną ultrafiltrację podczas 16-godzinnej wymiany dializacyjnej, co wskazuje na jego potencjalną przydatność w leczeniu pacjentów z ciężką zastoinową niewydolnością serca z lub bez współistniejącej schyłkowej niewydolności nerek.

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