Enhanced Mass Transfer in Peritoneal Dialysis with Application of Ultrasound


Peritoneal dialysis is one of several renal replacement therapies for kidney disease patients. The authors applied ultrasound to enhance the rate of peritoneal mass transfer. In vitro permeation experiments were performed with the parietal peritoneum taken from a rabbit. A small piece of the peritoneum had been set between the donor and receptor compartments of a membrane permeation system, which was completely submerged in a water bath of an ultrasonic cleaner. Experiments were performed with or without application of ultrasound. Average rates of enhancement were 160 and 150% for creatinine by application of ultrasound of 28 and 45 kHz, respectively. These findings implied that the application of ultrasound should directly change the permeability of the parietal peritoneum. In vivo experiments were also performed with rabbits placed in a water bath of a large ultrasonic cleaner under anesthesia. Rates of peritoneal transport in vivo for urea and creatinine were also enhanced to 159, 113, and 83% for urea and were 149, 112, and 94% for creatinine (n=3) on the average with application of ultrasound of 28, 45, and 100 kHz, respectively. No significant change in ultrafiltration, however, was found between the results with ultrasound and those without ultrasound, which may suggest that the ultrasound possibly increase the local blood flow rate that could increase the net ultrafiltration.

Introduction

Peritoneal dialysis is a therapy alternative for end-stage renal disease patients and continuous version of the peritoneal dialysis is termed Continuous Ambulatory Peritoneal Dialysis (CAPD). The treatment consists of continuous presence of washing solution, called dialysate, in the peritoneal cavity. Dialysate is an electrolyte solution with various concentration of glucose (usually 1.36%, 2.35%, 3.86%) as an osmotic agent that causes osmotic flow of excess water from the body fluid to the dialysate. Dialysate is changed every 6 hours, 4 times a day by the patient every day. Since CAPD has many clinical advantages against classic hemodialysis therapy, it is accepted by more than 60 thousand patients world wide.

One of the major clinical problems in long-term CAPD is the decrease of amount of ultrafiltration for removing excess water from a patient body. Recent studies show that some intermittent treatment, such as NIPD (Nightly-intermittent PD) and/or DAPD (Daytime Ambulatory PD) may be preferred in which no dialysate is loaded during night-time or day-time, respectively. Since these treatments change dialysate fluid with shorter time-intervals, amount of net ultrafiltration may increase in each dwelling, which results in an improved removal of excess water. However, since contacting period of dialysate with the peritoneum in these treatments is significantly shorter than that in CAPD, insufficient solute removal may be caused with these treatments. The authors then introduced ultrasound for enhancing the rate of peritoneal mass transfer for the period when dialysate is indwelling, and termed phonophoretic peritoneal dialysis. In this paper studies were performed both in vitro and in vivo in rabbits for demonstrating effects of peritoneal mass and water transport by application of ultrasound.

Materials and Method

In vitro experiments

Two pieces of small interstitial part of the parietal peritoneum was torn off from the peritoneal cavity of an euthanized Japanese white rabbit (male, BW 2.0–2.5 kg, Seiwa experimental animal Co., Oita, Japan), and they were separately placed between the donor and receptor compartments of a membrane permeation sys-

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Fig. 1. In vitro membrane permeation system in an ultrasonic cleaner (SUS-103, Shimadzu Co., Kyoto, Japan).

A piece of the parietal peritoneum was set between the donor and receptor compartments in the membrane permeation system. Donor and receptor solution were mixed by a pair of magnetic stirrers.

tem, specially designed for this experiment. The entire system was completely submerged in a water bath of an ultrasonic cleaner (SUS-103, Shimadzu Co., Kyoto, Japan, Fig. 1). A 30 ml of saline and the same amount of a saline creatinine solution was put into the receptor and donor compartments, respectively. Rotating speed of the magnetic stirrer to mix the donor and receptor solutions was set at 2000 rpm. A series of membrane permeation experiment was performed for one hour with application of ultrasound of 0 kHz (no ultrasound) followed by 28 kHz, and the other with 0 kHz followed by 45 kHz at 37°C. Each experiment was performed twice for different parietal peritoneum taken from a different subject.

In vitro experiments

Japanese white rabbits were anesthetized with 25 mg/kg-BW of sodium pentobarbital (Nacalai tesque Inc., Kyoto, Japan). All hair around the abdomen was shaved and a straight peritoneal catheter was implanted. One hundred and fifty ml of test solution, which contained high concentrations of urea and creatinine (approximately 214 mg/dl and 15 mg/dl, respectively), was prepared by 1.36%-glucose dialysate (Dianede®, Baxter Healthcare Co., U.S.A.) and small amount of normal saline. Osmotic pressure of the test solution (approximately 330 mOsm/kg-solvent) was set slightly higher that in blood of the subject so that only limited amount of net water transport would be expected due to osmotic gradient during the course of normal transfer study. Since bidirectional peritoneal transport has been already reported,4,5 a normal transport (from the test solution to the body fluid) study was made for two hours at room temperature (control study). After completing the control study, the test solution in the peritoneal cavity was completely drained. Then the subject was placed in a water bath of an ultrasonic cleaner (W-115H, Shimadzu Co., Kyoto, Japan, Fig. 2). The same amount of the new fresh test solution was again put into the peritoneal cavity of the same subject, and the same experiment as the control one was performed for two hours at 37°C, applying ultrasound of 0 (no ultrasound), 28, 45, and 100 kHz at its maximum total power of 300 W (trial study).
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**Fig. 2.** *In vivo* peritoneal mass transfer enhancement study with a large ultrasonic cleaner (W-115H, Shimadzu Co., Kyoto, Japan).

A rabbit was submerged in a water bath of the ultrasonic cleaner. Experiment was performed at 37°C for two hours.

**Theoretical**

**In vitro experiment**

Rate of mass transfer through a piece of membrane from the donor compartment to the receptor compartment can be described by the following equation:

\[
\frac{d(V_{\text{DON}}C_{\text{DON}})}{dt} = \frac{d(V_{\text{REC}}C_{\text{REC}})}{dt} = KA(C_{\text{DON}} - C_{\text{REC}})
\]

(1)

where \(A\) is the effective membrane surface area [cm\(^2\)], \(C\) is the concentration of the solute of interest [mg/ml], \(K\) is the overall mass transfer coefficient [cm/min], \(t\) is the experimental time [min], \(V\) is the volume of a compartment [ml] and subscripts DON and REC represent the donor and receptor, respectively. Assuming \(V_{\text{DON}} = V_{\text{REC}} = V = 54.0\text{ ml} = \text{constant, Eq. (1)}\) may be easily solved to give:

\[
\ln \left( \frac{C_{\text{DON}} - C_{\text{REC}}}{C_{\text{DON}}(0) - C_{\text{REC}}} \right) = -\frac{2KA}{V}t
\]

(2)

Eq. (2) was used to fit experimental data, and the slope \((-2KA/V)\) was directly compared for evaluating enhancement of the rate of solute transport by ultrasound.

**In vivo experiment**

Since solutes of interest should penetrate from the test solution (dialysate) into the body fluid (blood) in these experiments, rate of peritoneal mass transfer can be expressed as follows in the absence of ultrafiltration:[5,6]

\[
\frac{d(V_{D}C_{D})}{dt} = -D_{B}(C_{D} - C_{B})
\]

(3)

where \(C_{B}\) and \(C_{D}\) are solute concentrations in blood and in dialysate [mg/ml], respectively, \(D_{B}\) is the peritoneal dialysance [ml/min], which is a function of both the peritoneal permeability and blood flow rate but is not dependent on concentrations, \(V_{D}\) is the amount of dialysate [ml]. Replacing \(C_{B}\) and \(V_{D}\) by their average values, i.e., \(C_{B}^*\) and \(V_{D}^*\), respectively, Eq. (3) may be solved to give:

\[
\frac{C_{D} - C_{B}^*}{C_{D}(0) - C_{B}^*} = \exp \left( -\frac{D_{B}}{V_{D}^*}t \right)
\]

(4)

where \(C_{B}(0)\) is the initial solute concentration in dialysate. Then plotting natural logarithm of the normalized concentration difference (left-hand side of Eq. (4)) against experimental time, a straight line with a slope of \(-D_{B}/V_{D}^*\) is expected. From the slope, \(D_{B}\) can be calculated as a mass transfer index. Then the transport enhancement factor was defined as follows:

\[
\frac{\text{Transport Enhancement Factor}}{D_{B}(w/o\ ultrason)} \times 100\ \%(\text{\%})
\]

(5)

The denominator of Eq. (5) is the \(D_{B}\) value obtained from the control study performed at room temperature.

Amount of ultrafiltration was evaluated by calculating average dialysate volume during the experiment. It is defined as follows, assuming the specific gravity of the solution to be unity:

\[
\frac{\text{Average test solution volume [ml]}}{2} = \frac{FBW + IBW + RSW - EBW}{EBW}
\]

(6)

where \(FBW, IBW,\) and \(EBW\) are the final, initial and empty bag weight, and \(RSW\) is the residual test solution weight in the peritoneal cavity in grams or milliliters.
### Results and Discussion

**In vitro experiment**

*In vitro* permeation experiments were made with an interstitial part of the parietal peritoneum. Example results for creatinine were shown in Fig. 3. Straight lines verified the validity of Eq. (2) and the slope of the line greatly changed with application of ultrasound. After performing the trial experiment with ultrasound, the last run was performed with no ultrasound (data not shown); however, the results were almost the same as the previous experiment with ultrasound. Also since no further change in slope was found by changing the rotating speed of a magnetic stirrer, the results found with ultrasound should not be caused by improved mixing condition of the fluid. Then it may be understood that the results were caused by the irreversible change of the permeability of the interstitial peritoneum.

**In vivo experiment**

Figure 4 shows example experimental results of the *in vivo* experiment for urea (top) and for creatinine (bottom). In this experiment, ultrasound of 28 kHz was applied in the trial study. Comparing slopes of the control and trial studies, it is understood that the rate of peritoneal mass transfer was enhanced by 1.6 times for urea and by 1.4 times for creatinine.

Experiments were repeated three times at each ultrasound frequency and all the results are summarized in Fig. 5. There found no big differences between urea and creatinine, although the molecular weight of creatinine (MW113) is almost twice as large as that of urea (MW60). The highest enhancement was found with ultrasound of 28 kHz. With the ultrasound of 100 kHz, average enhancement factors were 83% and 94% for urea and creatinine, respectively, which were even smaller than those found in the control studies. McLaughlin *et al.* also reported the similar results employing their 20 kHz-fixed ultrasound system. Although no reasonable explanation may be given for the
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Reduced peritoneal transfer with ultrasound, it could at least be stated that the rate of peritoneal transfer is dependent on the frequency of ultrasound and may be controlled by changing the frequency non-invasively.

According to the results for urea and creatinine, glucose, the osmotic agent, transport from the test solution (dialysate) into the body fluid, may have been also enhanced by ultrasound application. If so, amount of net ultrafiltration should have decreased by approximately the same order as the increase of creatinine transfer because the effective osmotic gradient is more quickly vanished. However, as shown in Fig. 6, no significant change in average volume of the test solution was found between the control and trial studies with application of various frequencies of ultrasound. Since water transport across the peritoneum is a function of blood flow or hydrostatic pressure as well as crystal and oncotic pressure gradient, ultrasound has possibly increased the local blood flow rate that could increase the net ultrafiltration because of increased hydrostatic pressure. Water transport across the ultra-small pore (radius≈4 Å), is primarily caused by oncotic pressure gradient, which should not change with change of local blood flow rate. Moreover, since the water transport across the peritoneum associated with the large pore (radius≈250 Å), generally contributes only about 10% of the total water transfer. Then observed enhancement of water transport by ultrasound should be done through the small pore (radius≈47 Å) which possibly causes enhanced mass transfer by convection. Then observed mass transport enhancement may have been associated with the increased blood flow rate (ultrafiltration rate) or increased permeability or both.

Conclusions

Although the system is still an experimental version and cannot directly be applied for patients, ultrasound can be a useful tool for enhancing the peritoneal transfer. From both in vivo and in vitro experiments, the following conclusions are withdrawn for phonophoretic peritoneal dialysis:

1. Ultrasound of an ultrasonic cleaner enhanced the rate of peritoneal mass transfer and the effects were dependent on the frequency of ultrasound.

2. In vitro experiments with ultrasound suggested that the ultrasound directly change the permeability of the interstitium of the peritoneum.

3. The rate of peritoneal mass transfer enhancement by ultrasound may be frequency-dependent and it can be controlled by changing its frequency without changing amount of net ultrafiltration.

References

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