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Peritoneal Ultrafiltration Dialysis: Enhanced Urea Transfer Using Hypertonic Peritoneal Dialysis Fluid *

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Peritoneal dialysis is generally considered to be a process of diffusion down concentration gradients. The passive nature of the peritoneal membrane has been well demonstrated by Boen (1) using solutions of varying compositions. In these studies solute transfer by diffusion is the only mechanism considered, and no distinction is made between solutions of differing osmolality.

The present study compares the rate of urea transfer using dialyzing solutions of different osmolalities (Table I). Solutions hypertonic to plasma enhance the transfer of urea across the peritoneal membrane and result in a markedly improved peritoneal clearance of this solute. The data suggest that solvent drag is the probable mechanism responsible for this effect.

Methods

Nine uremic subjects that required treatment by peritoneal dialysis were studied on the Clinical Research Center at the University of Pennsylvania. Disposable commercially available peritoneal dialysis equipment was used throughout. Points of difference from usual dialysis technique as described by Flanigan, Henderson, and Merrill (2) have to do with the timing of the various phases of each exchange. The time from starting inflow to the completion of drainage constitutes one exchange. This time was held as closely as possible to 70 minutes total. Each exchange was divided into inflow, dwell, and outflow time corresponding to the time required to run two bottles of dialysis fluid into the abdomen, the time during which dialysis fluid remains quiescent in the peritoneal space, and finally the time allotted for drainage of the dialysis fluid. Arbitrary times were selected for each phase. The outflow time was set at 30 minutes. Inflow time plus dwell time was set at 40 minutes. A usual inflow time for the equipment used was 10 minutes. Minor variations in inflow time were adjusted by modifying the dwell time so as to maintain the 40-minute total.

The volume of dialysis fluid in each of nine bottles was measured and found to average 1,038 ml ± 9.45.[1] Thereafter, two bottles were used for each exchange, and the volume was assumed to be 2,076 ± 18.9. Heparin (10 mg) and KCl (8 mEq) were added to each exchange for a total additional volume of 5 ml. Table I shows the composition of the dialysis fluid used.

Dialysis fluid temperature before infusion was maintained constant at 38° C by a constant temperature bath kept near the bedside. The volume of dialysis fluid drained from the patient was measured in a 2-L graduated cylinder and read to the nearest 10 ml.

Two types of clearance study were carried out. Type I was comprised of a control period utilizing dialysis fluid containing 1.5% glucose followed by an experimental period in which a 7.0% glucose solution was used. A final control period terminated the study. At least two and usually three exchanges comprised a period. Once a study was started, sequential exchanges were used, and no time was allowed to elapse between them.

In the Type II study urea was added to dialysis fluid containing either 4.25%[2] or 7.0% dextrose in an amount that equaled or exceeded the blood urea concentration. One exchange was then carried out using this solution.

In order for a peritoneal dialysis to be considered technically acceptable for clearance study, certain criteria had to be met: first, a freely running system as manifested by an inflow time of 15 minutes or less and virtually complete return of fluid (75-ml maximum retained) in 30 minutes of two preliminary exchanges conducted with no dwell time using dialysis fluid containing 1.5% glucose; second, agreement of the control exchanges before and after the experimental exchanges from the standpoint of effluent volume and degree of equilibration; and third, absence of fluid leak about the catheter as

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[1] All dialysis fluid used in the present study was kindly supplied by Abbott Laboratories, King of Prussia, Pa.

[2] One L each of dialysis fluid containing 1.5% and 7.0% dextrose was used to make the 4.25% dextrose solution.

TABLE I

*Composition of dialysis fluid**

Solute	Calculated	
	mEq/L	*mOsm/L*
Sodium	140.5	140.5
Calcium	3.5	1.8
Magnesium	1.5	0.8
Chloride	101.0	101.0
Lactate	44.5	44.5
Dextrose	*mmoles/L*	
1.5%	83.0	83.0
4.25%	236.0	236.0
7.0%	389.0	389.0

* All solutions used in these experiments were kindly supplied by Abbott Laboratories as Inpersol.

judged by wetting of a gauze sponge placed on the skin about the site of catheter insertion.

Specimens of dialysis fluid for analysis were taken from the drainage bottle at the conclusion of the outflow time. This technique avoids the error inherent in sampling a nonhomogeneous solution in the abdomen. Blood samples were drawn before and after both control and experimental periods. Osmolality determinations were carried out on a Fiske model G osmometer. Blood urea nitrogens were done with the direct nesslerization method of Simmons and Gentzkow (3). All determinations were done in duplicate.

A standard clearance formula (4) was used to express the results in the first type of study for both control and experimental periods.

$$C = \text{clearance (milliliters per minute)} = c_d V_d / c_b t,$$

where c_b = urea concentration (milligrams per 100 ml) in blood; c_d = urea concentration (milligrams per 100 ml) in dialysis fluid; t = time in minutes required to complete one exchange; and V_d = volume of dialysis fluid (milliliters) returned at the end of an exchange.

In the second set of experiments where urea was added to hypertonic dialysis fluid the clearance resulting from ultrafiltration was calculated as follows:

C_{uf} = ultrafiltration clearance (milliliters per minute) $= (c_{d_0} V_{d_0}) - (c_{d_1} V_{d_1})/c_b t = c_{uf} V_{uf}/c_b t$,

where c_{d_0} = concentration in milligrams per 100 ml of urea in the effluent dialysis fluid; V_{d_0} = volume in milliliters of effluent dialysis fluid; c_{d_1} = concentration in milligrams per 100 ml of urea in the dialysis fluid before infusion; V_{d_1} = volume in milliliters of dialysis fluid before infusion; c_{uf} = concentration of urea in the solution that is transferred across the peritoneal membrane in response to hypertonic dialysis fluid; and V_{uf} = volume of ultrafiltrate (milliliters) calculated as the volume of dialysis fluid returned from the patient minus the volume of hypertonic dialysis fluid infused.

Results

In the first study five clearance determinations were carried out in four different subjects. Table II shows results from a representative experiment. Exchanges 4, 5, 9, 10, and 11 represent control observations using dialysis fluid containing 1.5% dextrose. Exchanges 6, 7, and 8 are experimental observations in which dialysis fluid containing 7.0% dextrose was used. There is good agreement between control dialysate volumes returned before and after the experimental exchanges. Rates for turnover of dialysis fluid (V_d/t) in the experimental exchanges of study A ranged from 39.3 to 40.6 ml per minute, as compared with bracketing control values approximately 10 ml per minute lower. The slightly lower rates for exchanges 9 and 10 reflect the longer exchange times. Figure 1 compares the turnover rates of dialysis fluid for each of the five studies. The range and mean value for each control and experimental period are given. As in study A, the

TABLE II

*Protocol and results from clearance study A**

Exchange no.	Time				Dialysate volume returned	V_d/t	% dextrose		c_d	c_b	c_d/c_b	C
	Inflow	Dwell	Outflow	Total			1.5	7.0				
	minutes				*ml*	*ml/minute*			*mg/100 ml*			*ml/minute*
4	12	28	30	70	2,215	31.6	x		89.4	137.0†	0.652	20.6
5	10	30	30	70	2,210	31.6	x		90.7	131.7†	0.689	21.8
6	12	28	30	70	2,755	39.3		x	93.1	126.2	0.738	29.0
7	10	30	30	70	2,840	40.6		x	89.4	120.9	0.739	30.0
8	12	28	30	70	2,800	40.0		x	86.9	115.3†	0.754	30.1
9	10	30	32	72	2,068	28.7	x		74.7	110.0	0.679	19.5
10	10	35	30	75	2,100	28.0	x		74.7	104.8	0.714	20.0
11	11	29	30	70	2,150	30.7	x		68.6	99.3†	0.691	21.2

* Abbreviations: V_d/t = turnover rate for dialysis fluid, c_d = urea nitrogen concentration in dialysis fluid at the end of an exchange, c_b = urea nitrogen concentration in blood (BUN), and C = peritoneal clearance for urea.
† Measured values. Other values for BUN are taken from a plot of BUN vs. time constructed from the measured points.

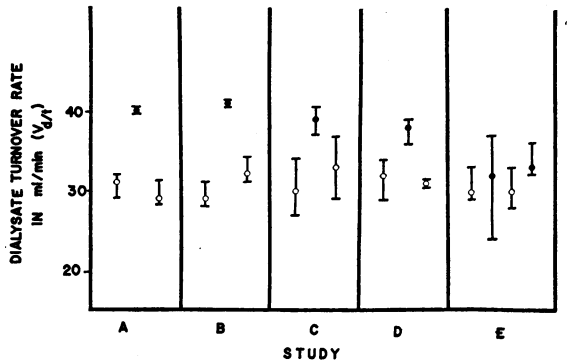

FIG. 1. THE RATE OF DIALYSIS FLUID EXCHANGE FOR FIVE STUDIES. Solid circles represent hypertonic (7% glucose) solutions as compared with control (1.5% glucose) values (open circles). The range for each mean is indicated.

control periods bracket the experimental periods. Every mean represents the values for at least two and usually three or more exchanges. As expected, in every instance the turnover rate for dialysis fluid containing 7% dextrose exceeded control values. In study E this increase was small perhaps because of peritoneal changes that may have resulted from two previous episodes of peritonitis.

The degree to which blood urea has equilibrated with dialysis fluid (c_d/c_b) at the end of an exchange in study A is indicated in Table II. This ratio is increased above control values in all three experimental exchanges. Figure 2 plots the range and mean values for c_d/c_b of control and experimental exchanges for each of the studies. With

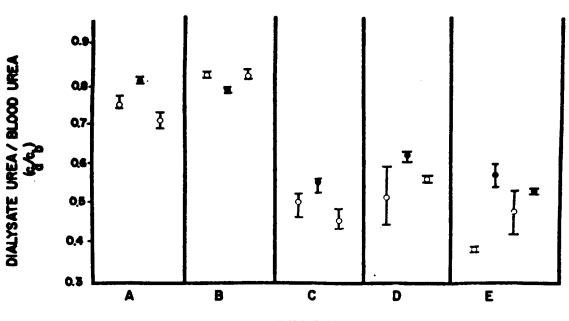

FIG. 2. RATIO OF OUTFLOW DIALYSATE UREA CONCENTRATIONS TO BLOOD UREA CONCENTRATIONS IN FIVE PATIENT STUDIES. Open circles represent control values obtained with dialysis fluid containing 1.5% glucose, and solid circles represent values obtained with fluid containing 7.0% glucose. The range for each mean is indicated.

the exception of study B higher values were obtained when 7% dextrose-containing solutions were used. The last column of Table II gives the peritoneal clearance figure for each exchange in study A. The mean clearance value for the experimental exchanges is 29.7 ml per minute. This is significantly different ($p < 0.01$) from the mean for the control exchanges of 20.6 ml per minute. Figure 3 plots the urea clearances in each of the five studies. Without exception the mean clearance values for experimental exchanges exceeded those of control exchanges ($p \leq 0.01$).[3] The over-all mean for per cent increase in clearance with hypertonic solutions is 38% above control values.

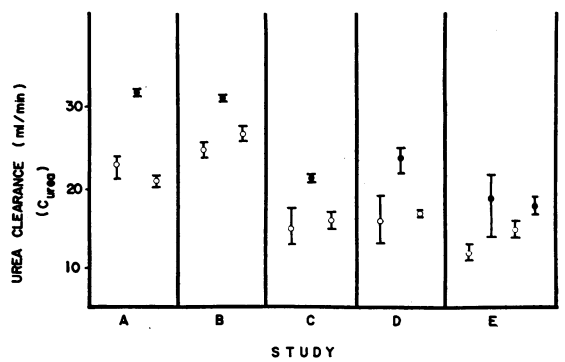

FIG. 3. UREA CLEARANCE WITH DIALYSIS FLUID CONTAINING 7% DEXTROSE (SOLID CIRCLES) COMPARED TO THAT WITH FLUID CONTAINING 1.5% DEXTROSE (OPEN CIRCLES) IN FIVE STUDIES. The range for each mean is indicated.

In the second study six experiments were carried out in four patients to determine the mechanism of this enhanced solute transfer with hypertonic dialysis fluid. In this group of experiments urea was added to dialysis fluid made hypertonic to blood by the addition of either 4.25% (studies III, V) or 7% dextrose. Table III shows the ratio of urea concentration in the dialysis fluid to that in the blood before installation of the fluid into the peritoneal cavity (c_d/c_b pre). These ratios ranged from 0.96 to 1.03, indicating virtually no concentration gradient between blood and dialysis fluid for urea. Figures for this ratio after completion of the 70-minute exchange are given in the column headed c_d/c_b post. In no study did

[3] The standard deviation for the difference of the means was calculated. The p value (5) in each study was equal to or less than 0.01.

TABLE III

*Removal of urea in the absence of a concentration gradient**

Study	c_d/c_b		V_{uf}	Urea removed	Osmolality		
					Dialysis fluid		
	Pre	Post			Pre	Post	Plasma
			ml	*mg*			
I	1.02	0.96	475	520	717	489	338
II	0.96	0.93	425	375	716	530	334
III	1.03	1.02	240	178	434	422	320
IV	1.01	0.97	650	437	700	448	310
V	1.00	1.00	310	350	548	423	348
VI	1.03	1.02	540	562	719	507	317

* Abbreviations: c_d/c_b pre = ratio of urea nitrogen concentration in dialysis fluid and blood before introduction into the peritoneal space, and post = ratio of urea nitrogen concentration in dialysis fluid and blood at the conclusion of the exchange; and V_{uf} = volume of dialysis fluid returned in excess of that infused.

this ratio change greatly. In studies III and VI this ratio remained slightly above 1, indicating if anything a concentration gradient for urea from dialysis fluid to blood at the close of the exchange.

Table III also lists the amount of ultrafiltrate [4] (V_{uf}) obtained in each study as the difference between infused and returned dialysis fluid volume. In studies III and V where 4.25% dextrose-containing solutions were used the volume of ultrafiltrate is lower than in the other four studies where the dextrose concentration was 7%. The amount of urea removed varied from 178 to 562 mg per 70-minute period. This figure is obtained as the difference in urea content between the infused and returned dialysis fluid. Finally, the osmolality of the dialysis fluid is listed before and after equilibration in the peritoneal space. Plasma osmolality measured at the conclusion of each study is given in the last column. Osmotic equilibrium was not reached in any study.

Discussion

In the first clearance studies dialysis fluid turnover rate (V_d/t) invariably increased in response to solutions containing 7.0% dextrose (Figure 1). This is expected and easily explained by movement of water down a concentration gradient established across the peritoneal membrane [5] by use of hypertonic dialysis fluid. In order for urea clearance to increase in the experimental period, the amount of urea transferred into the dialysis fluid must increase as well. This increase may not be apparent if the concentration ratio for urea (c_d/c_b) is considered alone as this value may fall from the control figure as a result of dilution. As noted above, this fall occurred in study B (Figure 2) in spite of an increase in the amount of urea transferred. The remaining four studies, however, show an increase.

There are several possible mechanisms for an increase in the transfer of urea observed with hypertonic solutions. The rate of diffusion may be enhanced. Theoretically, this could result from an alteration in membrane permeability. Mean effective pore size could have increased in response to tissue dehydration imposed by the steep osmotic gradient from tissue to dialysis fluid. Another possibility is that an increase in effective capillary membrane area could have resulted from the irritant properties of the hypertonic solution producing vascular dilatation in the peritoneal membrane. In addition, such dilatation by supplying more urea to the blood side of the membrane might shorten the distance over which the gradient for urea operates. Dilution with ultrafiltrate of the urea transferred by diffusion is another mechanism by which the driving gradient would be enhanced. (As previously noted, this last mechanism could only play a role in study B.) All the mechanisms so far mentioned rely on diffusion. Net movement by diffusion implies a concentration gradient down which solute or solvent can move. The second group of experiments (type II) was designed to establish whether simple

[4] Ultrafiltrate refers to the water plus solute that is transferred across the peritoneal membrane in response to hypertonic dialysis fluid.

[5] Peritoneal membrane is here defined to include all tissue and fluid media separating blood and dialysate.

diffusion could fully explain the increase in solute transfer observed. In this group of experiments urea was placed in hypertonic dialysis fluid in sufficient concentration to obliterate or reverse the usual blood to dialysis fluid gradient. In Table III a value of 1 or more for the ratio of dialysis fluid urea to blood urea at the beginning of an exchange (c_d/c_b pre) indicates no concentration gradient or a gradient favoring uptake of urea from the dialysis fluid by the patient. In this situation urea moved into the dialysis fluid and was removed from the patient (Table III), clearly invoking a transport mechanism beyond simple diffusion as a possible explanation.

In none of the experiments was dialysis fluid left in the peritoneal space long enough for osmotic equilibration to occur (Table III). Flanigan and co-workers (2) report osmotic equilibration for 4.25% solutions as occurring at 30 minutes. This was not found to be the case in the present study or in a subsequent larger series studied by Flanigan (6).

The addition of urea to the dialysis fluid in excess of that present in the blood establishes a concentration gradient for urea from dialysis fluid to blood. Any movement of urea in this direction will tend to mask the movement of urea in the reverse direction (i.e., from blood to dialysis fluid). To state this another way, a concentration gradient for urea from dialysis fluid to blood increases the back diffusion of urea and, depending on the magnitude of the gradient, the direction of the net urea movement across the peritoneal membrane can be changed from blood to dialysis fluid (as in the present experiments), to no net flux, or from dialysis fluid to blood. Adjusting the concentration of dialysis fluid urea to equal that of blood throughout the period of equilibration would give the most accurate estimate of urea transferred into the dialysis fluid during the equilibration with 7% dextrose-containing dialysis fluid. In the present group of experiments the concentration ratio for urea (pre c_d/c_b) was kept low (1.03 maximum) to gain the best estimate of the amount of urea transferred.

A passive mechanism that is capable of moving solute in the absence of a concentration gradient is required to explain the data. Such a mechanism has been described in other biological systems (7). It involves postulating the entrainment of solute particles in a solvent stream (solvent drag). This implies movement of water by bulk flow rather than diffusion. This mechanism pertains only under nonsteady state conditions where a concentration gradient exists for solvent. The evidence for bulk flow in the present experiment is indirect. Confirmation will require the demonstration that actual water movement across the peritoneal membrane in response to a concentration gradient far exceeds that predicted from isotopic data for diffusional movement.

TABLE IV

*Peritoneal ultrafiltration clearance for urea**

Study	V_{uf}/t	c_{uf}/c_b	C_{uf}
			ml/minute
I	6.34	0.79	4.94
II	6.08	0.81	4.92
III	3.43	0.93	3.19
IV	8.67	0.86	7.45
V	4.43	1.00	4.43
VI	7.73	0.95	7.33

* Abbreviations: V_{uf}/t = turnover rate for ultrafiltrate, c_{uf}/c_b = concentration ratio for ultrafiltrate and BUN, and C_{uf} = peritoneal ultrafiltration clearance for urea.

The concentration of urea in the ultrafiltrate (c_{uf}) can be calculated from the figures for urea removed and the volume of the ultrafiltrate, both of which are given in Table III. Table IV lists the urea concentration ratios of ultrafiltrate and blood (c_{uf}/c_b) for each of the six type II studies. These figures indicate the degree to which urea is sieved out of the solvent stream by the membrane. If no urea were sieved out the ratio would be 1. The urea clearance for ultrafiltrate (C_{uf}) can be calculated by using the turnover rate (V_{uf}/t) and the concentration ratio (c_{uf}/c_b).

The respective contributions of diffusion and solvent drag in the situation where 7% dextrose-containing dialysis fluid is used can be obtained indirectly from the present data if it is assumed that the increment in clearance noted in the first experiment is a result of both solvent drag and enhanced diffusion, and that in the second experiment the contribution of diffusion has been effectively blocked by the addition of urea to the dialysis fluid leaving only solvent drag as a driving force. By subtracting the ultrafiltration clearance from the increment in clearance above control values noted in the first experiment, we can obtain the contribu-

tion of diffusion. The mean value[6] for ultrafiltration clearance is 6.2 ml per minute. The mean increment in clearance noted with 7% dextrose-containing dialysis fluid in the type I experiments is 7.1 ml per minute. The discrepancy of only 0.9 ml per minute obtained as the difference between the ultrafiltration clearance and the clearance increment in the type I experiments suggests that the contribution of diffusion to the enhanced solute transfer noted with dialysis fluid containing 7% dextrose is small compared to that of solvent drag.

Clinically peritoneal ultrafiltration dialysis affords a means for increasing the efficiency of urea removal. Close attention to intravenous fluid and electrolyte replacement will be required. Of particular interest is the speculation that the technique of ultrafiltration so effectively utilized by the kidney at the glomerular membrane may result in the more efficient removal of solutes that classically have been difficult to remove by hemodialysis because of their slow rate of diffusion. Hydrated solute radius and pore size would provide the limiting factors. Support for this speculation can be found in ultrafiltration studies carried out on synthetic membranes in this laboratory and elsewhere.

Summary

Five peritoneal clearance studies comparing dialysis fluid containing 1.5% glucose with that containing 7% glucose showed enhanced removal of urea with the latter solutions.

A second set of six experiments conducted with hypertonic dialysis fluid containing urea in concentration greater than or equal to that of the patient's blood showed movement of urea into the dialysis fluid in the absence of a demonstrable urea gradient.

The data are best explained by postulating that the peritoneal membrane is porous in nature, and that fluid moves across it by bulk flow rather than diffusion. Solvent drag could then be invoked to explain the greater transfer of urea observed with hypertonic dialysis fluid.

[6] The two studies using a mixture of 7.0% and 1.5% (III and V) glucose solutions were excluded from the mean as 7% solution only was used in the type I experiments.

Acknowledgment

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