Effects of Dwell Time, Volume of Dialysis Fluid, and Added Accelerators on Peritoneal Dialysis of Urea

STANLEY C. PENZOTTI* and ALBERT M. MATTOCKS

Abstract ☐ The effects of variables of procedure in peritoneal dialysis on the urea clearances obtained were evaluated by means of a full factorial experiment. Three levels of each variable (dwell time, dialysis rate constant *via* additives in the solutions, and dialysis fluid volume) were used in all combinations. Results were subjected to an analysis of variance, which showed each variable to have a significant effect on clearance. Only one two-factor interaction was found to be significant. The applicability of basic kinetic equations for prediction of urea clearances in peritoneal dialysis was demonstrated by computing clearances for the same conditions as used in the experiment.

Keyphrases ☐ Peritoneal dialysis of urea—effects of dwell time, volume of dialysis fluid, added accelerators, statistical analysis ☐ Urea—peritoneal dialysis, effects of variables in procedure, statistical analysis ☐ Dialysis, peritoneal—statistical analysis of effects of procedure variables

Peritoneal dialysis is an effective method used to remove endogenous poisons and to treat symptoms of uremia. The procedures used, however, vary with the different clinics and clinicians, and there seems to be little substantial evidence by which one might select the best operating conditions.

Some details of the dialysis procedure have been examined and specific recommendations have been made. Fine *et al.* (1) studied continuous dialysis, varying the rate of flow of dialysis fluid on the individual patient, and concluded that maximum clearance was obtained at a flow rate of 40–60 ml./min. Boen (2) studied the clearance of urea as a function of the rate of inflow of dialysis fluid and obtained a maximum clearance at an inflow of 3.5 l./hr. (58 ml./min.). Similar maxima were obtained at approximately the same flow rates for several other substances, including creatinine, uric acid, potassium, magnesium, phosphate, and sulfate. Boen (2) recognized that the apparent fall in clearance above 3.5 l./hr. might be an artifact due to a small number of measurements. Miller *et al.* (3) compared several techniques for peritoneal dialysis, including one procedure with a 10-min. period for the introduction of the fluid, zero dwell time, and a 15-min. drainage period. This procedure gave no greater clearance than the control method with a 25-min. dwell time. Other techniques, with inflows up to 100 ml./min., gave only modest improvements. Gross and McDonald (4) found the temperature of the dialysis fluid to be important; increases of 35% in urea clearance were obtained by warming the fluid to 37°.

The general tendency has been to use a volume of dialysis fluid of 2 l. without question, presumably because this amount is convenient and not large enough to cause patient discomfort. The time the fluid is allowed to remain in the abdomen varies with the clinician, usually from 30 min. to 1 hr., although shorter periods are sometimes encountered.

The question of choice of operating variables is of particular concern when substances are evaluated for acceleration of dialysis. For example, a substance that accelerates diffusion across the membrane would be expected to give the same clearance as the control if the dwell times were long enough for the establishment of equilibrium. Conversely, the shorter the dwell time, the more effective the accelerator might appear to be.

In selecting the volume of dialysis fluid to be used for each exchange, it would appear that the larger the volume the greater would be the clearance, since dialysis across the membrane is a function of concentrations in the two compartments and a larger volume would yield a larger amount.

Typical unanswered questions arise: Is it better to use a small volume of fluid and exchange it more rapidly or to use a large volume with longer dwell time? Is there an optimum time–volume ratio? Would there be a significant advantage in using a more rapid inflow and outflow of dialysis fluid?

Many questions concerning techniques involve more than one factor and represent, in statistical terms, questions about two-factor interactions. As a first attempt to answer such questions, a factorial experiment was run on the removal of urea by peritoneal dialysis. The full factorial design enables one to evaluate both the main effects of variables and the interactions of two factors at a selected number of levels.

It was thought also to be of value to determine whether the process of dialysis might be predicted by mathematical expressions; to this end, the same experiments were "run" on the computer.

EXPERIMENTAL

Selection of Variables—Three levels of each variable were selected to cover as broad a range as possible. Volumes of dialysis fluid were: V_1, 35 ml./kg.; V_2, 65 ml./kg.; and V_3, 100 ml./kg. Dwell times were: D_1, 0 min.; D_2, 30 min.; and D_3, 60 min. Accelerators were selected on the basis of previously evaluated rate constants (5); they were: K_1, control fluid consisting of dextrose (1.5%), sodium lactate (0.5%), sodium chloride (0.56%), calcium chloride (0.026%), and magnesium chloride hexahydrate (0.015%) in distilled water, with an apparent dialysis constant of 0.01 min.$^{-1}$; K_2, control fluid with 0.01% cetyltrimethylammonium chloride added, with an apparent constant of 0.026 min.$^{-1}$; and K_3, control fluid with 0.01% dioctyl sodium sulfosuccinate added, with an apparent constant of 0.041 min.$^{-1}$. All combinations of three levels of the three variables, V, D, and K, were tested, comprising a full factorial experiment of 3^3 or 27 experiments.

Intermittent Dialysis Procedure—Healthy, mature male rabbits were used, with no general anesthesia but with a 50-mg. intramuscular dose of chlorpromazine hydrochloride 1 hr. prior to the experiment. The animal was weighed, a urinary catheter was inserted, and 400 mg./kg. of ^{14}C-tagged urea was injected intravenously. This injection consisted of 4.7 mg. of ^{14}C-urea (specific activity 4.65 mc./mmole) plus 2 g. urea and 0.9 g. benzyl alcohol in sufficient water for injection to make 100 ml. One hour

Table I—Observed Clearances with Variations in Fluid Volume, Dwell Time, and Added Accelerators[a]

Set 1		Set 2		Set 3	
Conditions	Clearance, ml./min./kg.	Conditions	Clearance, ml./min./kg.	Conditions	Clearance, ml./min./kg.
$V_2D_2K_2$	1.188(0.873)	$V_2D_3K_2$	0.562(0.591)	$V_3D_2K_2$	1.417(1.343)
$V_3D_3K_2$	1.108(0.910)	$V_1D_2K_2$	0.594(0.470)	$V_3D_3K_3$	1.211(0.944)
$V_3D_2K_1$	0.684(0.736)	$V_2D_2K_1$	0.644(0.478)	$V_2D_3K_1$	0.455(0.417)
$V_2D_3K_3$	0.771(0.613)	$V_3D_2K_3$	1.596(1.552)	$V_2D_2K_3$	1.031(1.009)
$V_1D_3K_1$	0.300(0.224)	$V_3D_3K_1$	0.635(0.642)	$V_2D_1K_2$	1.533(0.869)
$V_1D_2K_3$	0.613(0.543)	$V_1D_3K_3$	0.362(0.330)	$V_1D_2K_1$	0.397(0.257)
$V_2D_1K_1$	0.532(0.350)	$V_2D_1K_3$	1.900(1.305)	$V_1D_1K_3$	1.102(0.703)
$V_3D_1K_3$	1.613(2.007)	$V_3D_1K_2$	1.756(1.338)	$V_3D_1K_1$	0.517(0.538)
$V_1D_1K_2$	0.770(0.468)	$V_1D_1K_1$	0.393(0.188)	$V_1D_3K_2$	0.453(0.318)
		Averages			
V_1	0.554(0.389)	D_1	1.124(0.863)	K_1	0.506(0.426)
V_2	0.957(0.723)	D_2	0.907(0.807)	K_2	1.042(0.798)
V_3	1.171(1.112)	D_3	0.651(0.554)	K_3	1.133(1.001)

[a] Computer-predicted values in parentheses.

was allowed for distribution of the exogenous urea throughout the body fluids; then the first dialysis fluid was introduced into the peritoneum *via* a previously inserted pediatric size peritoneal catheter. The dialysis fluid was injected in a few seconds by use of 50-ml. syringes filled in advance. The fluid was allowed to remain in the peritoneum for the prescribed dwell time; then drainage was started, allowing the fluid to drain through a 1-m. length of plastic tubing which hung down from the operating table into a graduated cylinder. In all cases, the drainage time was 10 min. Blood samples were taken from the marginal ear vein at the time of introduction of each dose of peritoneal fluid and at the end of the experiment. The volume of dialysate returned was noted in each instance, the fluid was mixed thoroughly, and a sample was taken for measurement. Repeated dialyses were performed over approximately 3 hr., thus utilizing 18 exchanges for 0-min., 5 for 30-min., and 3 for 60-min. dwell times.

Measurement of ^{14}C in Samples—One-half-milliliter samples of plasma and 1-ml. samples of dialysate were pipeted into counting vials, 10 ml. of counting fluid was added directly, and the vials were counted on a liquid scintillation counter, using the channels ratio method for quench corrections. The counting fluid consisted of a mixture of 2,5-diphenyloxazole, 4 g./l., and 1,4-bis-2(5-phenyloxazolyl)benzene, 0.3 g./l., in a solvent of 2 parts toluene and 1 part Triton X-100[1]. Results were calculated in terms of concentration, micrograms per milliliter, of exogenous urea in the sample.

Treatment of Data—Clearance values were selected to express results, since these values are customarily used in the clinic. For each exchange of dialysis fluid, the urea clearance was calculated by the well-known formula:

$$\text{clearance (ml./min.)} = \frac{UV}{P} \qquad \text{(Eq. 1)}$$

where U is the concentration of urea in the dialysate, V is the volume of dialysate collected divided by the cycle time (*i.e.*, the dwell time plus drainage time), and P is the average plasma concentration (mean of samples at beginning and end of the cycle). For each experiment, the clearances for individual cycles were averaged and divided by the weight of the animal to obtain values of milliliters per minute per kilogram. The clearances would be expected to vary with animal weight since the volume of dialysis fluid was determined on basis of weight.

Computer Predictions—Computer calculations used the equations of Rescigno and Segre (6) for plasma and dialysate concentrations at a given time:

$$X_1 = \frac{X_0}{m_2 - m_1}\left[(k_2 - m_1)e^{-m_1t} + (m_2 - k_2)e^{-m_2t}\right] \qquad \text{(Eq. 2)}$$

$$X_2 = \frac{X_0k_1}{m_2 - m_1}\left(e^{-m_1t} - e^{-m_2t}\right) \qquad \text{(Eq. 3)}$$

where X_1 is the plasma level at time t, X_0 is the initial plasma level at the beginning of dialysis, $k_1 = k_2 =$ dialysis rate constant, m_1 and m_2 are the roots of the auxiliary equation, and X_2 is the dialysate concentration. For this purpose, an average plasma level of 450 mcg./ml. was used as X_0, k_1 was taken as equal to k_2 since free diffusion is assumed in both directions, and an average value of excretion constant from previous experiments (0.0002 min.$^{-1}$) was taken as k_3. The values of m_1 and m_2 were calculated from the equations:

$$m_1 = \frac{q - \sqrt{q^2 - 4k_2k_3}}{2} \qquad \text{(Eq. 4)}$$

$$m_2 = \frac{q + \sqrt{q^2 - 4k_2k_3}}{2} \qquad \text{(Eq. 5)}$$

where $q = k_1 + k_2 + k_3$.

First the plasma level at the beginning and end of each cycle was computed. Then the dialysate concentration at the end of each minute of drainage was calculated, and this value was multiplied by one-tenth the dialysis fluid volume to predict the amount of urea removed each minute of drainage. These values were accumulated over the 10-min. period to get the total amount removed. Finally, the clearance was calculated. The process could be repeated over a number of exchanges, but a single cycle gave the same result. The computer program assumed perfect drainage at a constant rate of one-tenth the volume per minute and instantaneous injection of peritoneal fluid. Changes in the urinary excretion constant over a broad range had little effect on predicted dialysis clearance values.

RESULTS

The average clearance values observed and those predicted by the equations are presented in Table I; an analysis of variance of the observed data is shown in Table II.

The experiments demonstrated that shorter dwell times significantly increased the clearance values, zero dwell time giving nearly double the average clearances obtained with 60-min. dwell periods.

The volume of dialysis fluid used in each exchange also had a pronounced effect, with the highest volume giving nearly double the

Table II—Analysis of Variances, Observed Clearances

Source	Sum Squares	*df*	Mean Squares	*F*
Volume, V	1,767,314	2	883,657	39.30[a]
Dwell time, D	1,010,060	2	505,030	22.46[a]
Accelerator, K	2,065,639	2	1,032,820	45.94[a]
$V \times D$	166,154	4	41,539	1.85
$V \times K$	318,820	4	79,705	3.54
$D \times K$	511,204	4	127,801	5.68[b]
Subtotal	5,839,191	18		
Total	6,019,065	26		
Residual	179,874	8	22,484	
Estimate of standard error = 0.150 ml./min./kg.				

[a] Significant at 1% level. [b] Significant at 5% level.

---

[1] Palmetto Chemical and Supply Co.

clearance of the lowest. The highest volume would, of course, be impractical for man, requiring 6 l. for a 60-kg. man. Whether any increase in volume over the 2 l. commonly used would be practical remains for the clinician to determine, but any significant increase would be useful.

The added accelerators were quite effective in increasing average clearances, with the intermediate giving double the clearance of controls. The fact that accelerators were effective regardless of dwell time and fluid volume points to the potential value of such agents. Since dwell time can be reduced no further and the volume of dialysis fluid cannot be increased beyond certain limits due to patient discomfort, the use of accelerators may be the most promising approach to the improvement of clearances.

The effects of D, V, and K were not linear; in each case, the difference was greater between the least effective and intermediate levels than between the intermediate and most effective levels.

With a few exceptions, the clearances observed followed the trends predicted by the application of the equations. The exceptions were chiefly failure to predict as high a clearance as was observed with zero dwell time. This result is thought to be due to the time required to introduce the dialysis fluid and start drainage, thus allowing for slightly more extended drainage times than intended. Also, since there was no control over the rate of outflow of the fluid, some errors would result from the assumption of constant drainage rate.

In a majority of instances, the equations predicted clearances lower than those observed. A better fit of the equations to the data could, no doubt, be made, but this was not the intent of the calculations; rather, it was the purpose to use K values from previous data and see how well the equations would predict clearances under a variety of conditions. Some difficulties of the experimental technique make it impractical to have actual conditions follow the assumptions required for the computations, thus making it prudent to utilize predictive equations for estimating relative values or trends rather than attempt to obtain accurate values for a given set of conditions.

It was surprising to find little evidence of interactions between factors, although it was pleasing to find such clear main effects. When the experiment was planned, it was thought that an accelerator might be useful only with short dwell times, which would appear as a $D \times K$ interaction. This effect was, indeed, detected but was significant only at the 5% level. The interpretation of this interaction is that the accelerator effect was greater at short dwell times (at $D = 0$ min., $K_2/K_1 = 3$; at $D = 60$ min., $K_2/K_1 = 2$), although the accelerator effect was significant at all dwell times. Since there were no duplicates of individual combinations of factors in this experiment, the three-factor interaction cannot be evaluated.

DISCUSSION

It was of interest to examine, by means of equations, the puzzling finding of Boen (2) that a maximum clearance is attained at dialysate flow rates of 3.5 l./min. For the lower flow rates, Boen used a 10-35-15 schedule, where the first number indicates the time in minutes for introduction of fluid, the second indicates the dwell time, and the third is the drainage time. For the higher flows, he apparently used a 10-5-15 schedule, thus having two exchanges of fluid in an hour.

By using Eqs. 2 and 3 and k's from the animal data as before, the concentrations in dialysate during introduction of fluid were calculated and the overall concentration upon complete introduction was estimated. This value was then referred to calculated concentrations which would have been obtained had the entire volume been introduced instantaneously; the corresponding time was taken as the adjusted time by which to calculate later dialysate concentrations. It was found that the 10-min. introduction period at a constant rate of inflow was equivalent to a 6-min. period if all fluid has been introduced at once. By using these adjusted time values, the amount removed in the dialysate was calculated as before.

By using 60 ml./kg. of dialysis fluid and assuming a 60-kg. man, the clearance predicted with the 10-35-15 schedule was 22.6 ml./min.; with the 10-5-15 schedule, it was 21.2 ml./min. These relative values agree with the observations of Boen (2) and demonstrate that under these conditions the clearance may be expected to decrease in spite of increased flow of dialysis fluid. It also shows that the reason for the decrease at higher flow rates is the greater amount of time involved in introducing and draining the fluid.

If the dialysis fluid can be injected in 1 min. and drained in 10, giving a 0-20-10 schedule, the predicted clearance would be 30 ml./min.; for a 0-50-10 schedule, it would be 25 ml./min.; for a 0-0-10 schedule, it would be 15 ml./min. Thus, even with instantaneous introduction of fluid, a maximum would be found due to the finite time required for drainage. By use of this type of calculation, it should be possible to estimate optimum operating conditions for whatever introduction times or drainage times one might find convenient.

REFERENCES

(1) J. Fine, H. H. Frank, and A. M. Seligman, *Ann. Surg.*, **124,** 857(1946).

(2) S. T. Boen, *Medicine*, **40,** 243(1961).

(3) J. H. Miller, R. Gipstein, R. Margules, M. Schwartz, and M. E. Rubini, *Trans. Amer. Soc. Artif. Intern. Organs*, **12,** 98(1966).

(4) M. G. Gross and H. P. McDonald, *J. Amer. Med. Ass.*, **202,** 363(1967).

(5) S. C. Penzotti and A. M. Mattocks, *J. Pharm. Sci.*, **57,** 1192 (1968).

(6) A. Rescigno and G. Segre, "Drug and Tracer Kinetics," Blaisdell, Waltham, Mass., 1966, p. 28.

ACKNOWLEDGMENTS AND ADDRESSES

Received February 1, 1971, from the *School of Pharmacy, University of North Carolina, Chapel Hill, NC 27514*

Accepted for publication June 18, 1971.

The authors acknowledge the assistance of Sherman Riggsbee in the laboratory.

* Present address: National Institutes of Health, Bethesda, MD 20014