KINETIC EVALUATION OF UREA AND POLYPEPTIDE CONCENTRATIONS IN UREMIA; THE LIMITS OF MANIPULATION WITH CURRENT THERAPY

F. A. Gotch and J. A. Sargent (Co-investigators), M. L. Keen,
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First Annual Progress Report
June 30, 1973 Through June 29, 1974

DIALYSIS TREATMENT AND RESEARCH CENTER
RALPH K. DAVIES MEDICAL CENTER
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Dialysis Treatment and Research Center
Ralph K. Davies Medical Center
Franklin Hospital
Castro and Duboce Streets
San Francisco, California 94114

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16. Abstracts A need for accurate measurement of dialysis parameters, in order to document, and prescribe therapies quantitatively can be met by a clinical model. Information was gained on urea generation, distribution, and the kinetics. A similar evaluation was made with polypeptide material. Limitations of single pool modeling have made necessary a multicompartment model, which was used to evaluate the apparent volumes of distribution, the rate of generation and the intercompartmental transfer coefficients of this material. Five uremic patients were treated sequentially at 6 month intervals with a cellulose hollow fiber kidney (CHFK), cellulose acetate hollow fiber kidney and CHFK. Observations on neuropathy, anemia and platelet function showed no change. The conclusion that these organ system lesions are unrelated to solute toxicity, however, cannot be justified since only a modest change in polypeptide concentrations would be predicted which could easily be overshadowed by dietary factors.

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SUMMARY

There exists a need for accurate measurement of clinical parameters in patients undergoing hemodialysis treatment. This need has two aspects:

1. Documenting of controlled experimental therapies to determine what change has been induced in independent concentration variables.
2. Enabling clinicians to prescribe therapies that will maintain their patients within what they consider acceptable limits.

These needs can in part be met by use of a functional clinical model of dialysis; its functionality depends, however, on the ability to measure and/or control all of the model parameters.

The use of a model has been evaluated in the case of urea and has resulted in the ability to establish the necessary patient parameters and, in fact, to predict the required value of treatment variables to control the clinical state of individual patients with respect to this solute. In the process of this evaluation, information has been gained with respect to urea generation, urea distribution, and the possible kinetics of urea in blood and how this may affect its removal in intermittent dialysis therapy.

A similar evaluation has been conducted with respect to a recently discovered polypeptide material. In a general sense, single pool analysis has allowed estimation of generation rate, volume of distribution and concentration levels of this material in chronic uremics and normals. By analyzing this substance, however, the limitations of indiscriminant single pool modeling have become apparent. From the concentration variation with time of this substance it has been determined that a multicompartment model must be used to evaluate the effect of dialysis therapy on lowering its body concentrations. A two pool model has been developed and used to evaluate the apparent volumes of distribution, the rate of generation and the inter-compartmental transfer coefficients of this material. Using these parameters the expected effect of different treatments has been investigated; two of the resulting

predictions are that there should be a schedule dependence of body concentration and that the lowest concentration in the non-perfused pool will not occur at the end of dialysis.

Using the in vitro characteristics of seven different dialyzers (1) the polypeptide material has been tentatively sized at between 500 and 600 Daltons, (2) the data suggests that inhibition of transport exists in non-cellulose membranes (i.e.: cellulose acetate, polycarbonate, and polypeptide). It is possible that this second observation may apply to other experimental membranes.

Five uremic patients on intermittent dialysis therapy (IDT) were treated sequentially at 6 month intervals with a cellulose hollow fiber kidney (CHFK), cellulose acetate hollow fiber kidney (CAHFK) and CHFK. Serial observations on neuropathy, anemia and platelet function showed no change. The conclusion that these organ system lesions are unrelated to solute toxicity, however, cannot be justified at this time: (1) In vivo clearance of polypeptide substances by these experimental dialyzers is far less than had been projected from in vitro data and (2) this material has been found to distribute in the body on the basis of more than one solute space. Consequently, only a modest change in polypeptide concentration would be predicted which could easily be overshadowed by other uncontrolled factors during dialysis such as increased generation due to dietary changes. (Constant polypeptide concentrations have in fact, been observed). The lack of change in uremic lesions would, therefore, be consistent with these findings.

EVALUATION OF HEMODIALYSIS THERAPY USING SINGLE POOL KINETICS FOR UREA

Introduction:

There exists a need for accurate measurement of clinical parameters in patients undergoing hemodialysis treatment. This need has two aspects:

1. Documenting of controlled experimental therapies to determine what change has been induced in independent concentration variables.

2. Enabling clinicians to prescribe therapies that will maintain their patients within what they consider acceptable limits.

These needs are evident throughout the field of hemodialysis research. Various research strategies have been proposed[1] and widely used involving lowered dialysate or blood flow rate[2-5] and large membrane area dialyzers[6-8]. High flux therapy has also been suggested and used to assess the effect of removal of large molecular weight solutes on uremic lesions[9,10]; to date, none of these therapies have resulted in any dramatic change in the magnitude of uremic lesions. In addition, efforts are currently being made to assess the possibilities of shortened dialysis time using high efficiency dialyzers[11-14]. These studies have been primarily based on the assumption that increased membrane area will result in proportional increase in middle molecule removal which in turn will allow for decreased treatment time[1]. Different therapy schedules exist from center to center, treatment covers the entire range from 12 to 36 hours a week,[15] and variation in treatment from one patient to another if it exists has generally been prescribed on a basis of clinical intuition.

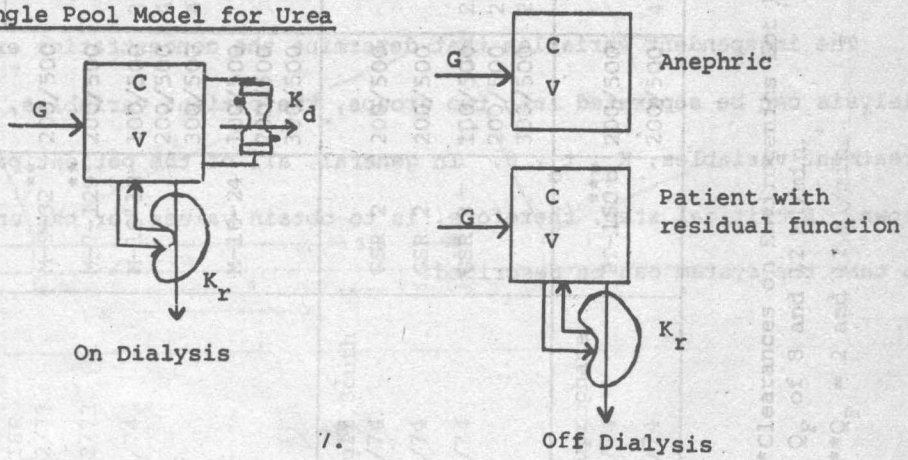
The prescription of therapy generally has been hindered by the lack of objective indicies of dialysis adequacy and within the range of therapies described above, no changes in traditional uremic lesions has been apparent. Consequently, it must be observed that uremia has been resistant to study by use of the empirical approaches described above.

Determination of Patient Parameters V and G

A rational view of hemodialysis therapy must rest on the premise that adjustment of blood concentrations is necessary for adequate control of uremic lesions; in this regard an appreciation of the variables that determine those concentrations is invaluable. Various models for the patient dialysis system have been developed[16,17]. These, however, cannot be of clinical utility unless the determining parameters are ammenable to clinical measurement and/or control. The desirability of applying kinetic modeling routinely to hemodialysis treatment is attractive and has led us to attempt clinical control using one of the simpler models.

Our first attempt to measure and then control hemodialysis therapy has been based on a model using single pool urea kinetics to analyze therapy. There are several advantages to this approach exclusive of the question of urea toxicity. Urea can be related to dietary protein intake and its generation is presumed to be related in some linear manner to other protein breakdown products. (We have found, as will be described below, that the rate of appearance of a polypeptide material does have a direct relation to urea generation). In addition, methods are widely available for routine determination of this substance which is the predominant solute encountered in uremia,and most centers keep records of urea levels on their patients. Finally, there is a wealth of information concerning urea, its generation, its distribution and its metabolism which makes its use as a marker substance for modeling of routine dialysis treatment attractive.

Figure 1. Single Pool Model for Urea



Above is shown the various aspects of single pool modeling of urea; extensive development of this model in a more general context has been covered elsewhere[18]. The basic elements of the analysis are shown in Table I which describes the time dependent concentration variation produced during intermittent therapy and shows the mathematical relationships which describe these fluctuations. It is evident that concentration drops rapidly during dialysis and increases slowly during the interdialytic interval. The rate and extent of these concentration oscillations will depend upon the volume of distribution of the solute in the individual patient (V) the rate at which the solute is being generated (G), the level of function, if any, of the patient's kidney (K_r), the dialyzer clearance of the solute (K_d), the length of dialysis (t_d) and the interval between dialysis (θ). With all of these variables established the concentration pattern for an individual patient will be fixed as long as none of these parameters change. This being the case, there will be a unique value for the adjustable variables that will keep an individual patient at a desired concentration level; (the predialysis concentration C_o has traditionally been selected as the critical concentration in hemodialysis therapy). Similarly when one of the variables is changed (for example, dialyzer clearance) the change required in the other parameters needed to keep C_o at the same level can be predicted.

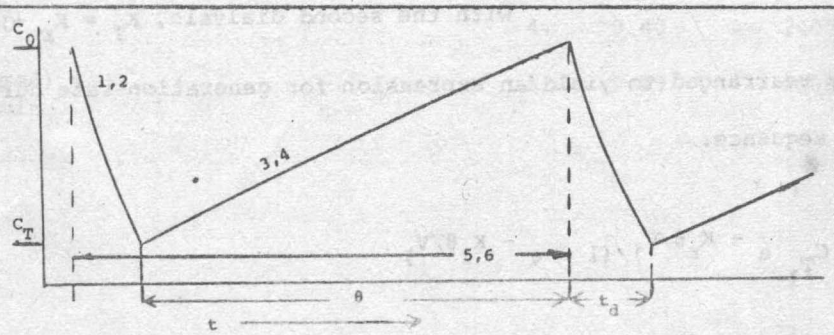
The independent variables that determine the concentration excursions during dialysis can be separated into two groups, the patient variables, V, G, K_r and the treatment variables, K_d, t_d, θ. In general, all of the patient parameters are not known. A critical step, therefore, is to obtain values for the unknown variables so that the system can be described.

TABLE I

KINETIC DEFINING EQUATIONS FOR THE RELATIONSHIPS BETWEEN BLOOD SOLUTE CONCENTRATION AND DIALYSIS TREATMENT

(From: Gotch,F., Sargent, J., Keen, M.L., Said, M., Foster, R. Comparative Treatment Time with Kiil,Gambro and Cordis-Dow Kidneys, Proc.Clin.Dial.&Transp.Forum, 3, 217, 1973)

CONDITION	DEFINING EQUATION
1. Intradialytic kinetic relationships for the anephric patient.	$C_T = C_0 \, e^{-\frac{K_d t_d}{V}} + \frac{G}{K_d}\left(1 - e^{-\frac{K_d t_d}{V}}\right)$
2. Intradialytic kinetic relationships for the patient with residual renal function.	$C_T = C_0 \, e^{-\frac{(K_r + K_d)t_d}{V}} + \frac{G}{K_r + K_d}\left(1 - e^{-\frac{(K_r + K_d)t_d}{V}}\right)$
3. Interdialytic kinetic relationships for the anephric patient.	$C_0 = C_T + \frac{G\,\theta}{V}$
4. Interdialytic kinetic relationships for the patient with residual renal function.	$C_0 = C_T \, e^{-\frac{K_r \theta}{V}} + \frac{G}{K_r}\left(1 - e^{-\frac{K_r \theta}{V}}\right)$
5. Mass balance over one full cycle (predialysis one dialysis to predialysis next dialysis) in the stable anephric patient.	$C_0 = \dfrac{G\left[\frac{K_d \theta}{V} + \left(1 - e^{-\frac{K_d t_d}{V}}\right)\right]}{\left(1 - e^{-\frac{K_d t_d}{V}}\right)K_d}$
6. Mass balance over one full cycle (predialysis one dialysis to predialysis next dialysis) in the stable patient with residual renal function.	$C_0 = \dfrac{G\left[\frac{1}{K_r + K_d}\left(e^{-\frac{K_r \theta}{V}} - e^{-\frac{(K_r + K_d)t_d}{V}} \cdot e^{-\frac{K_r \theta}{V}}\right) + \frac{1}{K_r}\left(1 - e^{-\frac{K_r \theta}{V}}\right)\right]}{\left(1 - e^{-\frac{(K_r + K_d)t_d}{V}} \cdot e^{-\frac{K_r \theta}{V}}\right)}$



The residual kidney function (K_r) can be independently determined by urine collection; V and G, however, must be established. During carefully controlled dialyses where C_T, C_o, K_d, K_r, t and θ are determined, equations 1 or 2 and 3 or 4 will represent a system of 2 equations in 2 unknowns which will yield values for V and G. Because of the difficulty in solving these expressions analytically for either V or G, iterative solutions have been used. The concentration at the beginning and end of the intra and interdialytic periods are required for the solution of these two equations. If pre and post dialysis concentrations were constant with any therapy, only these two values would be needed. Because dialyses are unequally spaced, however, no single value of pre or post dialysis concentration will be unique. Consequently, the concentration that define each segment of the actual therapy curve are required. For this purpose two sequential dialyses are normally used although only the end dialysis concentration of the first dialysis, or alternatively the predialysis concentration of the second dialysis, is required, to obtain the three values that define the cycle. Equation 2 is rearranged to yield an expression for volume of distribution during a two dialysis sequence:

(7)

$$V = -K_T t_d / \ln \left[(C_{T_2} - G/K_T)/(C_{o_2} - G/K_T) \right]$$

Where C_{T_2}, C_{o_2} are concentrations associated with the second dialysis, $K_T = K_r + K_d$

Equation 4 is rearranged to yield an expression for generation rate during the same two dialysis sequence:

(8a)

$$G = K_r (C_{o_2} - C_{T_1} e^{-K_r\theta/V})/(1 - e^{-K_r\theta/V})$$

In the case of an anephric patient, this relationship becomes:

(8b) $G = (C_{o_2} - C_{T_1})V/\theta$

With knowledge of θ, t_d, K_d, K_r, C_o and C_T for the current and previous dialysis (i.e., C_{T_1} and C_{T_2}) equations 7 and 8 are solved in sequence using an assumed value of G which is corrected during subsequent calculations until G and V converge to their actual values. For example, if G is assumed to be 6 mg/min then V can be calculated from equation 7 ; using this value of V, G can be determined from equations 8a or 8b . This value is then used in equation 7 and the procedure continued until the value of G converges. For values of K_d for urea in the range of most current dialyzers these expressions converge rapidly even when the initial assumption of G is in error by over 100%. An example of such calculation and the values of V and G as the calculation proceeds through successive loops are shown in Table II; the rate at which the values of V and G converge are shown in Figure 2.

Table II

Calculation of V and G by Iteration

Known Patient and Treatment Parameters		Loop	G	V
C_{o_2} = 1.20 mg/ml	C_{T_1} = 0.16 mg/ml	1	6	25866
C_{T_2} = 0.16 mg/ml	K_r = 1.5 ml/min	2	10.01	23712
K_d = 160 ml/min	θ = 3000	3	9.26	24124
t_d = 360		4	9.40	24024
G (assumed) = 6 mg/min		5	9.39	24061

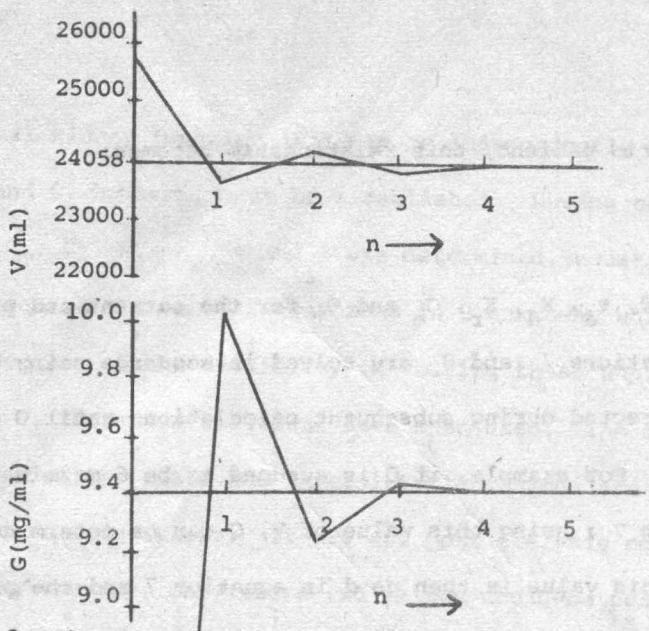


Figure 2. Convergence of V and G through 5 loop iteration

When clinical data are available for a number of dialyses, average values of volume ($\bar{V}$) and generation rate ($\bar{G}$) may then be calculated and will then be available for prediction of concentration as a result of therapy change. Such calculations have been made on 19 patients using normal clinical pre and post dialysis chemistries, recorded values for t_d and θ, and assumed dialyzer clearance; these values appear in Table III.

Values of $\bar{V}$ that appear in the table are in the range that in general would be expected for urea distribution if this solute were distributed in total body water[19] ($\bar{V}/W = 63\% \pm 8$). This is generally felt to be the case[20].

The values in Table III do appear in several cases to slightly exceed expected total body water and in a number of cases show large variations. It is probable that the higher than expected average distribution volumes result from over estimation of kidney clearance. K_d assumed > K_d actual indicates that more urea is being removed than is actually the case, consequently artificially high volumes will result from the above calculation. Such differences have been observed and will be discussed below. If such overestimates are consistent from one therapy to another, this overestimate of volume will not introduce significant errors. The variability in V

TABLE III

AVERAGE UREA DISTRIBUTION VOLUME AND GENERATION IN 19 PATIENTS AS CALCULATED FROM SINGLE POOL KINETICS

Patient	N	$\overline{G}$	Percent Stand Dev	$\overline{V}$	Percent Stand Dev	$\overline{V}/\overline{W}$
L.W.	2	5.8	2.4%	47.7	14%	76.2%
S.L.	3	4.9	10.1%	33.5	2%	57.7%
L.T.	8	7.9	19.4%	35.9	7%	67.5%
L.W.	3	6.3	1.6%	27.6	11%	51.7%
L.C.	6	5.3	12.8%	35.9	13%	73.4%
C.B.	2	8.2	5.1%	43.2	5%	52.7%
B.P.	2	7.0	3.0%	43.6	4%	74.0%
F.L.	4	6.5	6.6%	30.7	13%	66.9%
F.P.	4	6.8	39.4%	49.7	9%	72.2%
S.F.	2	5.9	30.9%	32.5	12%	59.4%
M.L.	5	6.1	19.5%	31.3	9%	55.8%
R.C.	7	4.7	25.8%	38.1	13%	71.9%
S.R.	9	6.9	18.5	30.9	14%	59.8%
E.T.	15	9.7	12.8%	33.5	5%	60.7%
R.A.	6	6.5	12.0%	39.4	7%	66.8%
W.F.	7	8.7	19.0%	40.3	8%	65.2%
R.B.	8	4.8	39.7%	38.8	9%	53.2%
V.B.	13	6.7	16.1%	33.9	10%	61.3%
H.N.	19	5.1	21.2%	35.8	17%	53.8%
Average		6.5	21.0%	37.0	16%	63.2%