Kinetic optimization of dialysis therapy

F. A. Gotch
R. K. Davies Medical Center. San Francisco (California).

The uremic syndrome is still poorly understood at the level of molecular toxicity. Dialysis therapy is largely empirical and based on the hypothesis that the accumulation of water and toxic solutes result in many of the manifestations of the uremic syndrome. The validity of this hypothesis has been demonstrated in part by the fact that dialysis therapy can result in long term amelioration of the uremic syndrome and has become an established therapy for uremia practiced world-wide. However, the uremic syndrome is only partly responsive to «adequate dialysis» and there is variable ongoing morbidity such as anemia, reduced taste and appetite, mild sensory neuropathy, renal osteodystrophy and pruritis in «well dialyzed» patients. There is still substantial intradialytic morbidity with a 10 to 30 % incidence of symptomatic hypotension. More recently a frequently disabling syndrome due to beta-2 microglobulin amyloidosis (AB2M) has been shown to occur frequently in long term dialysis therapy.

Kinetic modeling of dialysis therapy provides an analytic method to rigorously prescribe and assess the delivery of quantified amounts of dialysis. The purpose of this paper is to assess the present status and anticipated future developments in the next decade of urea, B2M, and heat modeling in dialysis therapy.

Urea kinetics

Calculation of the dose of dialysis is complicated both conceptually and technically. In dialysis therapy a clearance pathway is provided for removal of toxic endogenous solutes and thus the dialysis dose is a dimensionless parameter, the fractional clearance of the volume of distribution of the dialyzed solute. The fractional clearance is defined as the product of dialyzer clearance (K) and treatment time (t) divided by the solute distribution volume (V) or as Kt/V. Calculation of the Kt/V prescription is thus dependent on several interacting parameters: solute distribution volume; level of protein intake; level of residual renal function; transport properties of the specific dialyzer used; blood and dialysate flow rates; ultrafiltration rate; and frequency of dialysis.

Clinical dialysis is a high technology therapy with many interacting variables which must be well controlled for assurance that the prescribed Kt/V has been fully delivered. Errors in blood flow rate and treatment time, inadequate dialyzer reprocessing, fistula recirculation and dialyzer clotting can, and not infrequently do compromise clinical delivery of the prescribed Kt/V. In addition to calculating the Kt/V prescription, it is important to do ongoing quality assurance (QA) of the clinical delivery of the prescribed Kt/V.

The protein catabolic rate (PCR, gm/day) controls several of the clinical manifestations of uremia. Inadequate protein intake can result in protein malnutrition and increased mortality [1] while excessive protein intake results in excessive rates of acid and phosphorous loading. Consequently an objective measure of PCR is very useful to the physician and renal dietician who regularly must assess this component of therapy.

Although detailed understanding of endogenous solute toxicity has not been attained, the fractional clearance of urea nitrogen required relative to PCR for optimal dialysis therapy has been empirically determined in a tightly controlled clinical study [2]. Thus urea nitrogen provides a clinically validated marker solute for calculation of an adequate dose of Kt/V, QA of Kt/V delivery and for monitoring dietary protein intake from PCR measurement [2]. Traditionally these important therapy parameters have been assessed with a single pool, variable volume (SPVV) urea kinetic model which is based on the rate equations describing urea nitrogen mass balance during the dialytic and interdialytic intervals [3]. Appropriate solutions of these modeling equations permit measurement of the exact relationships between predialysis BUN, Kt/V, the normalized protein catabolic rate (NPCR, gm/(V/.58)/day) and the PCR. In this way all four of these critical parameters can be determined to assess adequacy of Kt/V relative to NPCR and adequacy of protein intake.

The SPVV urea model is a simplification of the kinetics of urea in dialysis therapy in that urea is

Correspondencia: Dr. F. A. Gotch.
R. K. Davies Medical Center.
San Francisco (California).

distributed in two compartments comprised of intracellular (Vi) and extracellular (Ve) water. The kinetics of urea transfer between these two compartments is first order and controlled by the whole-body cell urea mass transfer coefficient, Kc, ml/min [3]. If the dialyzer urea clearance, K, is quite high relative to Kc, the rate of urea removal from Ve during dialysis will exceed the rate of transfer from Vi and result in end dialysis dysequilibrium with substantially higher urea concentration in Vi relative to Ve. In this case the post dialysis BUN will be spuriously low and will rapidly rebound upward immediately after dialysis as urea diffuses from Vi to Ve down the concentration gradient. The spuriously low post dialysis BUN will result in calculation of an erroneously low V and erroneously high values for Kt/V and NPCR with the SPVV model.

The SPVV model results in minimal dysequilibrium and errors in V, Kt/V and NPCR when the ratio K/Kc $\leq$ .20, the typical case for conventional dialysis with t $\cong$ 3.5 hr.

The average normalized Kc (NKc, ml/min/L of V) is quite high, approximately 22 ml/min/L and in patients with an average level of NKc the ratio K/Kc increases to $\sim$ .35 when Kt/V of 1.1 is delivered in 2.0 hrs with high flux dialysis which will result in 5 to 10 % rebound of post dialysis BUN. If more rapid dialysis is performed or NKc is substantially less then 22 ml/min/L, the BUN rebound will increase and result in increasing underestimation of V and overestimation of Kt/V and NPCR calculated with the SPVV model.

The SPVV kinetic model errors will be minimal and adequately compensated in patients with average levels of NKc if the minimum Kt/V prescribed is 1.1 when NPCR = 1.1 and the minimum time for delivery of this dialysis dose is 2.0 hrs. We have recently observed suspiciously low values for V and high values for NPCR in a small number of patients on high flux (HF) dialysis suggesting significant double pool rebound despite the above constraints on dialysis rate. Post dialysis rebound studies have shown NKc values as low as 11 ml/min/L in some of these patients. Consequently the coming decade will very likely see incorporation of double pool correcting algorithms in the SPVV therapy model. In patients for whom algorithm corrected V is still less than 90 % of the value expected from surface area, it may be necessary to determine NKc from post dialysis rebound measurement.

Although SPVV modeling of HF dialysis can result in prescription evaluation errors in some instances, it is reassuring that the errors are in part self cancelling. The overestimation of NPCR will usually result in calculation of a higher Kt/V requirement. There is a risk of both underdialysis and inadequate protein intake, however, if dietary counselling to reduce protein intake is done in response to an overestimated NPCR.

AB2M kinetics

The plasma concentration of B2M, CpB2M, is increased 20 to 50 fold over normal in dialysis patients. This reflects the steady state production of approximately .1 mg/min and extrarenal clearance of approximately .002 L/min which results in CpB2M of approximately 50 mg/L [4, 5]. These markedly elevated blood levels suggest that AB2M formation is due to retention of B2M and at least in part CpB2M dependent. The advent of HF membranes permeable to B2M raises hope that B2M removal can reduce the rate of AB2M formation by reducing the time average concentration of CpB2M.

Beta-2-microglobulin is distributed in a volume approximating Ve [4, 5] in monomeric form [6]. Because of this small distribution volume, CpB2M will vary greatly as a function of interdialytic Na and H_2O accumulation and intradialytic removal. It will also vary greatly with relatively small changes in any residual renal function. For example, if residual renal clearance is .004 ml/min, the CpB2M in an average patient would be expected to be only .1/.006 or 17 mg/L rather than the 50 mg/L expected in the anephric patient.

It is likely that there has been considerable variability in the clearance of B2M provided in clinical studies to date due to less precise membrane production standards for B2M permeability compared to the high precision for urea permeability. The molecular size of B2M is near the membrane cutoff so that small differences in production control could be expected to substantially influence B2M permeability.

There is no knowledge at present about the kinetics of B2M polymerization to AB2M. The factors controlling the rate and sites of polymerization are of great importance but unknown at present.

During the next decade it is likely that substantial advances in understanding of AB2M and, it is hoped, retardation of its rate of formation will be achieved. This will require studies of the polymerization process and kinetically guided clinical studies with precise membrane permeability which account for distribution kinetics, volume changes and residual renal function. With hemodiafiltration it should be possible to reliably achieve Kt/V B2M levels in the range of 2.0. Long term clinical observations will be required to assess the effect of this level of treatment on the devastating clinical syndromes due to beta-2-microglobulin amyloidosis.

Heat kinetics

Maggiore was the first to recognize that substantial quantities of heat could be lost in isolated ultrafiltration and hemofiltration (IUF, HF) and to demonstrate that symptomatic hypotension was no greater in

hemodialysis (HD) compared to IUF and HF if core temperature (T) were stabilized during hemodialysis[7, 8]. However despite this striking benefit, lowered dialysate temperature is not frequently employed in HD, largely because patients experience thermal discomfort.

In an attempt to assess the magnitude of dialyzer heat flux required to stabilize T during HD, we formulated and solved a one compartment model of heat kinetics during HD[9]. This model was used to analyze literature data which showed that skin surface heat loss decreases 25 % when dialyzer heat removal is zero and that 45 % of the resting heat production must be removed by the dialyzer to stabilize and prevent a rise in core temperature expected to prevent heat accumulation, block the rise in body temperature with resultant warm shock amplification loop and substantially ameliorate symptomatic hypotension complicating 10 to 30 % of dialyses. It is hoped that in the coming decade on line thermal control systems will be developed for optimal control of thermal energy balance during dialysis.

References

1. Acchiardo S, Moore L and Latour P: Malnutrition as the main factor in morbidity and mortality of hemodialysis patients. *Kidney Int* vol. 24, suppl. 16:S199-204, 1983.
2. Gotch F and Sargent J: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 28:526-534, 1985.
3. Gotch F: Kinetic Modeling in Hemodialysis. In Nissenson, Gentile and Fine (Eds.): *Clinical Dialysis,* 2nd ed., Appleton & Lange, 319-330, 1989.
4. Vincent C, Pozet N and Resillard J: Plasma B_2-microglobulin turnover in renal insufficiency. *Acta Clinica Belgica* 35:suppl. 10:1, 1980.
5. Karlsson F, Groth T, Sege K, Wibell L and Pererson P: Turnover in humans of B_2-microglobulin: the constant chain of HLA-antigens. *European J of Clin Invest* 10:293, 1980.
6. Messner R: B_2-microglobulin: and old molecule assumes a new look. *J Lab Clin Med* 104:141, 1984.
7. Maggiore Q, Pizzarelli F, Sisca S et al.: Blood temperature and vascular stability during hemodialysis and hemofiltration. *Trans ASAIO* 28:523-527, 1982.
8. Maggiore Q, Pizzarelli F, Zocalli C et al.: Influence of blood temperature on vascular stability during hemodialysis and isolated ultrafiltration. *Int J Art Organs* 8:130-134, 1985.
9. Gotch F, Keen M and Yarian S: An analysis of thermal regulation in hemodialysis with 1 and 3 compartment models. *Trans ASAIO,* 1989 (in press).
10. Guyton A: *Textbook of medical physiology,* 6th ed. New York, W. B. Saunders Co., 886-897, 1981.
11. Maeda K, Morita H, Shinzato T et al.: Role of hypovolemia in dialysis-induced hypotension. *Artif Organs* 12:116-121, 1988.