Kinetic Modeling of "Go Slow" Dialysis in Acute Renal Failure

Remi O. Hombrouckx,[1] Dirk S. De Wachter,[2] Pascal R. Verdonck[2]

Werken Glorieux,[1] Dialysis Unit, Ronse; Hydraulics Laboratory,[2] Institute Biomedical Technology, University of Gent, Belgium

Go slow" dialysis is a gentle, intermittent hemodialysis therapy for acute renal failure patients, with advantages compared to slow, continuous therapies. It employs a recirculating closed dialysate circuit. A two-pool urea kinetic model is elaborated to determine kinetic parameters from blood and dialysate concentrations. This will allow quantification of the therapy. Variable clearance is included to accurately describe the kinetic process. The model is tested in an acute renal failure patient. Solute removals, as determined from direct dialysis quantification and by the model, are comparable. Variable clearance is not required to determine the kinetic parameters, because the constant mean clearance delivers equal results. The dialysis dose, as defined, allows comparison with chronic renal therapies. It requires solute removal determined from dialysate sampling and time-averaged concentration (TAC) from the urea kinetic modeling. In the test patient, dialysis dose is lower compared to standard thrice-weekly therapies because of its lower efficiency and higher TAC, a result of his highly catabolic state.

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Key words

Kinetic modeling, acute renal failure, "go slow" dialysis, two-pool kinetics, dialysis dose

Introduction

Acute renal failure can be treated by different clinical strategies, either in a continuous fashion or intermittently. For extracorporeal treatment, hemodialysis, hemofiltration, or a combination of the two modalities can be used. Continuous therapies have the advantage of mimicking the physiological situation, while imposing only mild stress on the critically ill patient. Although pumpless arteriovenous configurations are possible, in order to achieve sufficient clearance in highly catabolic patients and controllable ultrafiltration in hemodynamically unstable patients, a blood pump is necessary (1). This complicates the setup; therefore, intensive care units, which have access to dialysis equipment, might as well use the reliable dialysis technology to achieve the required treatment.

Correspondence to:
Remi Hombrouckx, MD, Werken Glorieux, Dialysis Unit, Hogerlucht 6, B-9600 Ronse, Belgium.

The "go slow" dialysis treatment is an adaptation of the classic hemodialysis strategy toward a more gentle but still intermittent removal of blood-soluble toxins and metabolic substances during the 4–10 hour daily treatments to avoid dialysis disequilibrium (2). For this treatment a single-needle dialysis apparatus is used, although a two-needle setup would also be viable. The double-headed single-needle setup (3) has the advantage that it requires only one single-lumen, central venous catheter for blood access. It can be placed in the subclavian, jugular, or femoral vein, depending on the patient's vasculature. All these sites are normally able to deliver peak flows of up to 300 mL/min, through 8 Fr catheters, as required by the single-needle operational mode to achieve the low mean blood flows of 80–150 mL/min. Also, the double-headed pump allows for small, controllable ultrafiltration rates, even with unstable arterial pressures. On the dialysate side, a closed recirculating loop is used, connected to a 40-L tank filled with bicarbonate dialysate. According to the individual needs, sodium, potassium, phosphate, oxygen, and glucose levels can be adjusted. This tank is refreshed every 2 to 4 hours, depending on the solute removal that is attained and the duration of the therapy. Specifically, the use of heparin in the dialysate fluid allows for sufficient anticoagulation at the artificial kidney membrane interface, without the need for high systemic heparinazation and consequent bleeding risks in the patient or regular flushing of the extracorporeal blood circuit.

In order to do the follow-up of these critically ill patients, monitoring of several metabolic parameters is necessary: fluid balance, acidosis, potassium levels, glycemic state, urea and uric acid concentrations, phosphate, etc. (4). Since urea is a marker for protein catabolism, it can be used to monitor the hyperalimentation and hypercatabolic state of acute renal patients. It is considered to be dangerous for critically ill patients to develop the uremic syndrome (5) and, therefore, requires continuous monitoring. Furthermore, urea is used as a marker for dialysis efficiency in classical chronic dialysis therapies. In the same manner, formal urea kinetics can be used as a prescription tool for acute renal failure therapies. The specific characteristics of "go slow" dialysis, however, present new problems that are not present with continuous therapies: intermittency accompanied with multicompartmental solute kinetics and nonconstant clearances because of the closed, recirculating dialysate circuit. In this paper we establish the necessary tools to evaluate a "go slow" dialysis session by urea kinetic modeling.

Material and methods

Kinetic model

To describe the urea concentrations in acute renal patients treated with "go slow" dialysis, a two-pool urea kinetic model with variable clearance is required. The model is schematically pictured in Figure 1. It includes an "internal" compartment (lowercase *i*), which is directly connected to the "external" compartment (lowercase *e*) and includes the vascular space from which solutes are removed in the dialyzer. The overall urea clearance of the dialysis therapy is noted by *K*, and *G* is the generation rate of urea. Mass transfer between the internal and the external compartments is symmetrically modeled by *M*. Volume changes by ultrafiltration are thought to influence both the internal and the external volumes equally because of the slow character of the ultrafiltration process. The percentage of the total distribution volume *V* that is taken in by the internal compartment (*Vi*) is expressed by the partition parameter ζ. The equations that describe the solute concentrations *Ci* and *Ce* as a function of time during dialysis are composed of two exponential functions:

$$Ci(t) = \alpha M\exp(-\lambda_1 t) + \beta M\exp(-\lambda_2 t) + G/K;$$

$$Ce(t) = \alpha(M - \lambda_1 Vi)\exp(-\lambda_1 t) + \beta(M - \lambda_1 Vi)\exp(-\lambda_2 t) + G/K.$$

In these equations the parameters α and β depend on the initial urea concentrations in both compartments, and the exponents λ_1 and λ_2 are functions of the clearance *K*, the mass transfer coefficient *M*, the volumes (*Vi* and *Ve*), the partition coefficient ζ, and the ultrafiltration rate. This equation is in a general form that can be used for both constant and variable clearances. In the case of variable clearance, the parameters α and β must be recalculated every time the clearance changes. To simplify the numerical calculus, the dialysis interval is divided in small time intervals during which clearance is considered to be constant.

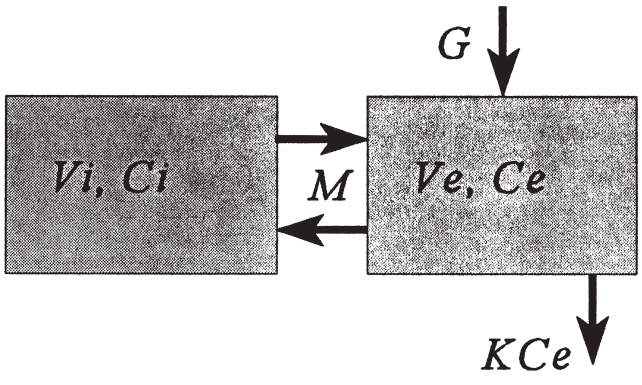

FIGURE 1 Two-pool urea kinetic model for "go slow" dialysis. *V* = volumes; *C* = concentrations; *G* = generation rate; *K* = clearance; *M* = mass transfer coefficient.

The variation of clearance is modeled according to the inlet concentrations of blood and dialysate. If, for example, the initial clearance K_0 with fresh dialysate is 100 mL/min, soon after the onset of dialysis the dialysate concentration of a solute will rise. This will decrease the diffusive transport across the membrane, since the logarithmic mean concentration difference will drop. For a first-degree approximation (with low dialysate concentrations), it can be assumed that the clearance will decrease linearly with the concentration difference of the inlet concentrations of blood C_b and dialysate C_d:

$$K = K_0 \frac{C_b - C_d}{C_b}.$$

After dialysis, the same equations can be employed, if the residual renal function is substituted for the total clearance *K* and the ultrafiltration rate replaces the water intake rate. The postdialysis rebound profile is mainly governed by the partition coefficient ζ, the intercompartmental mass transfer coefficient (*M*), and the urea generation rate (*G*). The latter has a more pronounced influence compared to patients with stable, chronic renal failure because of its high value in hypercatabolic acute renal failure patients. The urea concentration profiles calculated with these equations for the parameters in Table I are plotted in Figure 2. It is clear that when dialysate is exchanged, there is a more pronounced drop in the blood (external compartment) concentration. This drop in blood concentration is related to increased clearance each time the dialysate is changed. The concentration in the dialysate shows an upside-down profile compared with the blood concentration. Only a slight variation is seen in the slope of the "internal compartment" for the variable clearance, because it constitutes the larger volume of the two, and it is hidden behind the slow intercompartmental transfer interface.

Patient treatment and protocol

To test the model, a case study is performed with an acute renal patient. In this patient, for every dialysis session, five blood concentrations were measured at preset times: predialysis, mid-dialysis, and postdialysis, followed by samples at 30 and 60 min after treatment. The patient underwent four dialysis sessions during 5 days, of which the first three were daily "go slow" treatments of 7, 4, and 6 hours, respectively, with mean blood flows of around 120 mL/min. The fourth treatment, executed on the fifth day, was a regular 4-hour dialysis session with a blood flow rate of 180 mL/min. The sampled blood concentrations during the "go slow" therapy are shown in Figure 3. Each time the dialysate tank was changed, a 10-mL sample was taken from the well-mixed solution for direct dialysis quantification (DDQ) (6). All samples from one dialysis session were mixed together in the clinical laboratory for determination of the total solute removal.

TABLE I Parameters used to calculate theoretical urea concentrations

Parameter	*Value*
Clearance *K*	108 mL/min
Initial concentration	198 mg/dL
Patient volume *V*	5326 L
Partition coefficient ζ	69%
Mass transfer coefficient *M*	450 mL/min
Generation rate *G*	279 mg/min urea
Dialysate change times	150, 300 min after onset
Dialysate volume	3 × 40 L
Time on dialysis	7 hours

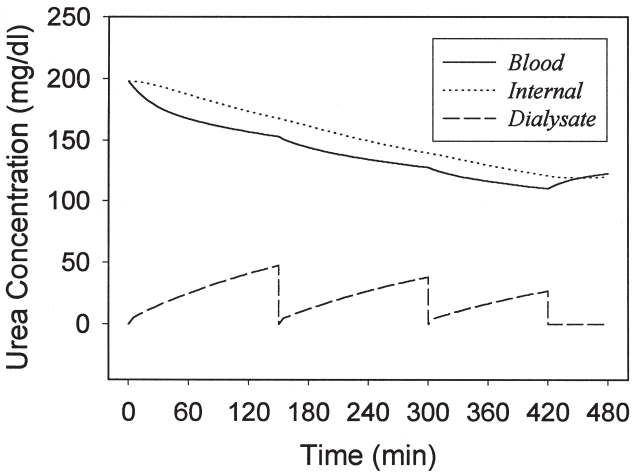

FIGURE 2 Theoretically determined urea concentration profiles in the blood and internal compartments and in the dialysate tank.

Dialysis efficiency is normally expressed by the dimensionless number Kt/V. However, this number does not allow comparison of daily dialysis strategies with regular thrice-weekly sessions. A more useful and kinetically valid number can be calculated with the solute removal (SR) normalized to the total mean solute content in the body (7) and is similar to Casino's approach for stable patients (8):

$$DD = \frac{SR}{TAC \times V}.$$

Dialysis doses (DD) can be obtained for single or multiple sessions. In the latter case the nominator is the sum of the removals during all the sessions, and TAC (time-averaged concentration) in the denominator is the mean concentration during and between all the dialysis sessions.

Results

The patient example was a 69-year-old male, weighing 84.5 kg. His residual renal function was negligible during the treatment period (<0.3 mL/min). The patient was treated with a cuprophane

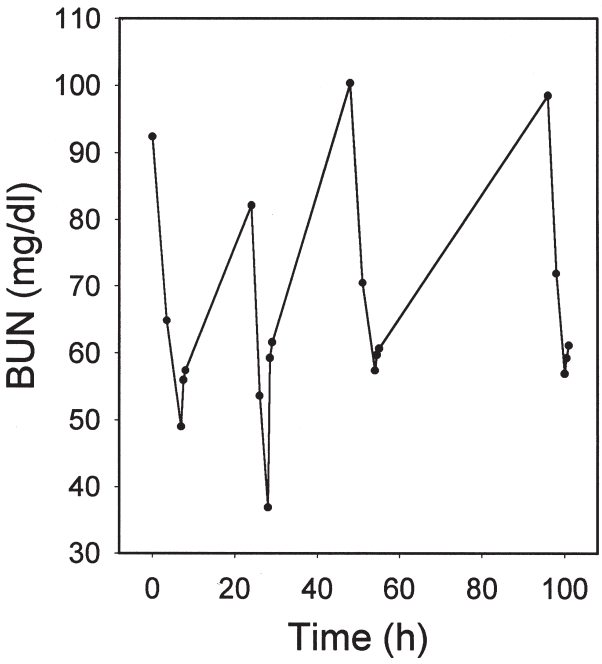

FIGURE 3 Blood urea nitrogen as measured during therapy in the patient.

1.9 m² dialyzer (Sorin, Mirandola, Italy). Ultrafiltration rates were set at 150–200 mL/hour. In Figure 4 the blood concentrations measured during one session are compared with the modeled urea concentration profiles. This session had a duration of 6 hours. The 40-L tank with bicarbonate dialysate was changed after 3 hours. Two different models are presented: one with a variable clearance related to the changes in dialysate concentration and a second with a constant clearance. In the first case the two-pool clearance varies between 104 mL/min (fresh dialysate) and 66 mL/min (at 3 hours). In the second model the constant two-pool clearance is 83 mL/min, which happens to be nearly equal to the mean clearance of the first model (82.9 mL/min). The other fitted parameters are tabulated in Table II. The fitted volume was limited to the value determined by anthropometric data (9).

Total solute removal as determined with both models is 47.6 g urea. The solute removal, as determined by DDQ, is only 43.0 g (79.86 L × 54 mg/dL). The modeled mean spent dialysate concentration is also 54 mg/dL.

When solute removal is determined by DDQ, TAC from urea kinetic modeling, and *V* by the Watson equation (9), the dialysis doses as calculated for the four acute dialysis sessions (depicted in Figure 3) are, respectively, 0.73, 0.35, 0.48, 0.48. When determined for the complete therapy, the dialysis dose becomes 1.59.

Discussion

From the results it appears that "go slow" dialysis can be equally modeled with or without variable clearance. Obviously,

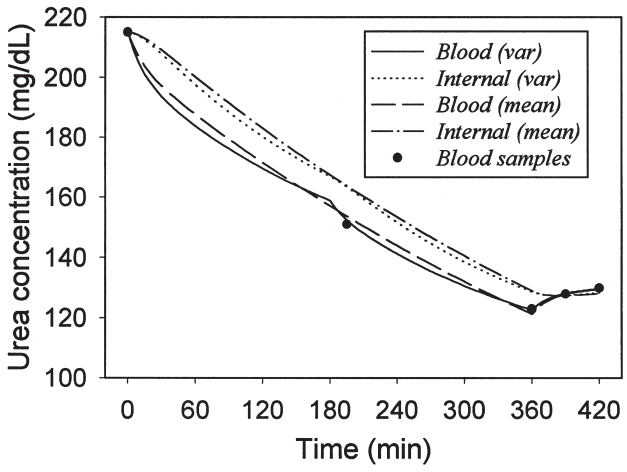

FIGURE 4 Fitted concentration profiles in the patient with (var) and without variable (mean) clearance.

TABLE II Fitted parameters for the patient

Parameter	*Value*
Initial concentration	215 mg/dL
Patient volume V	47 L
Partition coefficient ζ	67%
Mass transfer coefficient M	750 mL/min
Generation rate G	169 mg/min urea

the second model is easier to use and delivers the mean two-pool clearance of the therapy. The calculated urea concentration profiles for the two models are quite similar. For both models a two-pool model is necessary to be able to account for the rebound that occurs after the therapy. The two-pool behavior is established within the first half hour of dialysis (Figures 2 and 4). After that, a steady state is reached during which the two concentrations both decline with a rather constant slope. Similarly, the volumes reequilibrate 30–60 min after cessation of dialysis. Although the "go slow" method is considered a rather gentle hemodialysis method that does not reveal any clinical signs of disequilibrium (2), the therapy still appreciably differs from continuous therapies. Not only will the intermittency introduce variable concentration levels, the concentration disequilibrium over the patient's body water space is non-neglectable. Disequilibrium has been associated with rapid dialysis; therefore, it was suggested limiting the urea reduction ratio (URR) of the initial treatments below 0.3 (3). However, this figure was formulated for standard short hemodialysis. Since the first "go slow" dialysis is executed over a much longer time, a higher URR can be achieved, without compromising the patient's state of health. Therefore, this limit value should be expressed as the maximum urea concentration gradient per unit of time to be useful for prescription. In this patient the single-pool URR of the first session was 0.40.

The dialysis dose that was obtained in this patient can be compared with results from chronic therapies. Imagine a 70-kg anuric patient (urea distribution volume 40 L), treated with 3 × 210-min hemodialysis sessions. If his normalized protein catabolic rate is 1.1, and single-pool Kt/V of the sessions 1.2, this would theoretically yield a TAC of 54 mg/dL. To have sufficient removal of the generated urea, total solute removal during one week would be 70.6 g. Thus DD is 3.22/week or 0.46 daily. The acute patient studied in this paper has a daily DD of only 0.32. This lower result can be attributed to the relatively short sessions (4 and 6 hours) and the use of the two-pool model, which results in a lower overall clearance. This is in contrast with the calculations in the chronic dialysis patient, whose kinetics were assumed to be single-pool. By increasing the treatment length to 8 or 10 hours, a similar dialysis dose could be obtained for the acute patient as is the case for the chronic patient.

Conclusion

A two-pool kinetic model has been employed to describe urea kinetics during "go slow" dialysis as treatment for acute renal patients. The kinetics can be adequately described with a constant clearance model, although, in reality, the clearance is variable because of the closed dialysate circuit. Dialysis dose can be obtained from DDQ measurements combined with the calculation of TAC from the kinetic model.

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