A two-compartment kinetic model for assessing dialysis dose in chronic hemodialysis patients

R. Lavecchia[1], E. Staffolani[2], A. Zuorro[1]

[1]*Department of Chemical Engineering, "La Sapienza" University, Via Eudossiana 18, 00184 Roma, Italy*

[2]*Department of Nephrology, "Tor Vergata" University, Via di Tor Vergata 135, 00133 Roma, Italy*

This paper reports the results of a kinetic study aimed at quantifying the efficiency of urea removal during a hemodialysis treatment. A mathematical model considering the distribution of urea into a constant-volume intracellular space and a variable-volume extracellular compartment was developed. The model was validated on a set of 68 dialysis sessions referring to 9 chronically dialyzed patients. Estimates of extracellular urea concentrations were accurate within ± 3%. The model was also used to calculate the urea reduction ratio and to compare predictions with those obtained by the single-pool model. The results indicated that the delivered dialysis dose can be significantly overestimated (up to 20%) if compartment effects are not considered.

Keywords: hemodialysis, urea kinetic modelling, dialysis dose

1 INTRODUCTION

Hemodialysis is the most common form of life-sustaining treatment for patients with end-stage renal disease. Several studies have shown a strong correlation between delivered dialysis dose and patient morbidity and mortality [1], but assessment of dialysis dose is not performed on a regular basis. The simplest way to do it is to measure blood urea levels during the treatment and calculate some related performance indicator. The two most popular indicators are the urea reduction ratio (*URR*), between pre- and post-treatment values, and the *Kt/V* index, where *K* is the urea clearance, *t* is the length of treatment and *V* is the volume of urea distribution. Dialysis is considered adequate if some specified target, for instance: *URR* >65% or *Kt/V* >1.3, is reached [2]. Although this approach provides useful guidelines for therapy, it suffers from one major weakness, being both *URR* and *Kt/V* derived from the simple single-pool model. In particular, since this model cannot account for compartment effects, inaccuracies may result in the estimated dialysis dose [3]. In order to improve reliability various corrections have been proposed for the *Kt/V* [4], but all on empirical ground.

In the light of the above, the purpose of this study was to develop a more realistic model for urea removal, and to compare the experimentally determined reduction in blood urea during a dialysis session with predictions from this and the single-pool model. We were also interested in evaluating differences in the efficiency of removal calculated by the two models.

2 EXPERIMENTAL

2.1 Hemodialysis Treatments

Hemodialyses were performed at the Nephrology and Dialysis Unit, Complesso Integrato Columbus, Rome, on nine patients (4 males and 5 females) with a mean age of 49.5 ± 12.4 years, and with no residual renal function (Table 1).

Table 1. Clinical data for the dialysed patients (q_{uf} is the ultrafiltration rate, pre- and post-BUNs refer to the start and the end of dialysis)

Patient	Age	Weight (kg)	q_{uf} (ml/min)	pre-BUN (mg/dl)	post-BUN (mg/dl)
1 (M)	63	63.5	15.8	77.4	25.8
2 (F)	64	53.9	10.9	95.0	28.1
3 (F)	41	53.6	10.8	81.3	20.5
4 (F)	39	58.2	17.9	81.7	22.1
5 (F)	35	50.9	9.7	69.6	24.7
6 (M)	51	76.9	12.9	58.7	21.3
7 (F)	67	79.1	10.8	73.9	23.2
8 (M)	38	87.7	18.2	62.0	27.0
9 (M)	48	76.9	14.3	64.5	21.2

Hospal INTEGRA® dialysis machines were used, with a blood flow-rate of 300 ml/min and a dialysate flow-rate of 500 ml/min.
The patients were dialyzed three times a week and the session length was 240 min. During each session blood samples for BUN measurement were taken at 0, 120, 240 and 270 min.

2.2 Urea Kinetic Model

The model developed to describe the kinetics of urea removal is illustrated in Figure 1.

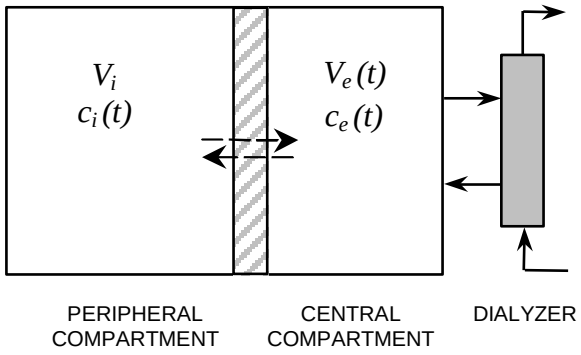

Fig. 1. The kinetic model

Urea is assumed to be distributed into a constant-volume intracellular space (peripheral compartment) and a variable-volume extracellular space (central compartment). An overall mass-transfer coefficient and an apparent clearance coefficient are used, respectively, to express solute transport between compartments and its elimination by the dialyzer. In addition, urea generation is assumed to occur intracellularly.
With these assumptions the mass balance for urea in the two compartments leads to the following differential equations:

$$V_i \frac{dc_i}{dt} = r_U V_i - AK_c(c_i - c_e) \quad (1)$$

$$\frac{d(V_e c_e)}{dt} = AK_c(c_i - c_e) - Kc_e \quad (2)$$

where c = urea concentration, V = compartment volume, r_U = urea generation rate, A = surface area, K_c = intercompartment mass-transfer coefficient, K = dialyzer clearance.

If the ultrafiltration rate, q_{uf}, is considered constant, V_e varies linearly with time:

$$V_e(t) = V_{e,0} - q_{uf} t \quad (3)$$

and integration of eqns. (1)-(2) with the initial conditions: $c_i(0) = c_e(0) = c_0$ provides the two functions $c_i(t)$ and $c_e(t)$.
The urea reduction ratio can then be calculated as:

$$URR = \frac{c_0(V_i + V_{e,0}) - (c_{i,f} V_i + c_{e,f} V_{e,f})}{c_0(V_i + V_{e,0})} \quad (4)$$

where the indices *0* and *f* denote initial and final quantities, respectively.
If ultrafiltration and urea generation are neglected, and if $AK_c >> K$, the single-pool constant-volume model is obtained:

$$V \frac{dc}{dt} = -Kc \quad (5)$$

and the quantity URR reduces to:

$$URR = \frac{c_0 - c_f}{c_0} \quad (6)$$

3 RESULTS AND DISCUSSION

Sixty eight dialysis sessions, for a total of 272 data points, were analysed. The experimental urea concentrations were determined from the measured BUN values as: c (g/l) = 0.0214 *BUN* (mg/dl).
We assumed that the total urea distribution volume at the end of each session, $V_i + V_{e,f}$, was 58% of the patient's dry weight. The urea generation rate was estimated, for each patient, from the final and the initial urea levels monitored in two consecutive sessions. On the average we obtained: 14.4 ± 0.18 mg/min. The ultrafiltration rate was calculated from pre- and post-dialysis weights, and the dialyzer clearance from the values provided by the manufacturer.
The unknown model parameters are: c_0, AK_c and $\gamma = V_i/V_{e,f}$. They were estimated, for each dialysis session, by minimizing the following objective function:

$$\Phi(\bar{\pi}) = \sum_{j=1}^{N} \left(c_{e,j}^{exp} - c_{e,j}^{calc} \right)^2 \qquad (7)$$

where $\bar{\pi}$ = parameter vector and N = number of data points. Minimization was carried out by a direct-search procedure coupled with a fourth-order Runge-Kutta method.

For the single-pool model, integration of eqn. (5) and minimization of Φ yield the two unknown parameters c_0 and K/V.

Estimates of c_0 by the model developed by us were very close to the experimental values (percent deviations <1%), whereas differences around 10% were obtained for the single-pool model. The three other parameters, AK_c, γ and K/V, averaged for patient, are summarized in Table 2.

Table 2. Estimated parameters for the two models (NS is the number of dialysis sessions analysed)

Patient	NS	AK_c (ml/min)	γ	K/V (min)
1	9	277 ± 102	1.94 ± 0.57	(3.68 ± 0.37) 10^{-3}
2	8	139 ± 57	2.25 ± 0.39	(3.78 ± 0.25) 10^{-3}
3	9	187 ± 99	1.62 ± 0.20	(4.54 ± 0.39) 10^{-3}
4	9	147 ± 43	1.56 ± 0.17	(4.39 ± 0.35) 10^{-3}
5	8	212 ± 58	2.50 ± 0.47	(3.46 ± 0.22) 10^{-3}
6	7	246 ± 43	1.53 ± 0.08	(3.51 ± 0.08) 10^{-3}
7	9	142 ± 34	1.61 ± 0.30	(3.91 ± 0.38) 10^{-3}
8	3	257 ± 74	1.53 ± 0.06	(2.78 ± 0.15) 10^{-3}
9	6	184 ± 75	1.65 ± 0.35	(3.83 ± 0.51) 10^{-3}
-	68	199 ± 52	1.80 ± 0.35	(3.76 ± 0.52) 10^{-3}

The values of γ are in good agreement with those determined using radiolabelled urea [5]. Estimates of AK_c are in the range of values: 93-300 ml/min found by Smye et al. [6], but are lower than those reported elsewhere. Published data, however, are widely scattered, which could indicate that this parameter is not only related to cell-membrane permeability, but also to treatment variables such as ultrafiltration rate and dialysate composition. This would suggest that perfusion may play some role in solute transport between compartments.

An important point to be noted is that the values of AK_c are very close to the dialyzer clearance, which is of the order of 200 ml/min. Therefore the hypothesis on which the single-pool model is based: $AK_c >> K$ is not fulfilled.

Typical results are presented in Figure 2, which shows a comparison between experimental and calculated blood urea concentrations for two dialysis sessions. As can be seen, the two-compartment model thoroughly describes the experimental concentration profiles, both during and after dialysis. By contrast, correlation by the single-pool model is very poor. The model, in particular, is not capable of reproducing the two main features of the experimental profiles: the initial rapid drop in concentration and the postdialysis urea rebound. This is not surprising, both aspects being related to compartment heterogeneity and delayed equilibration.

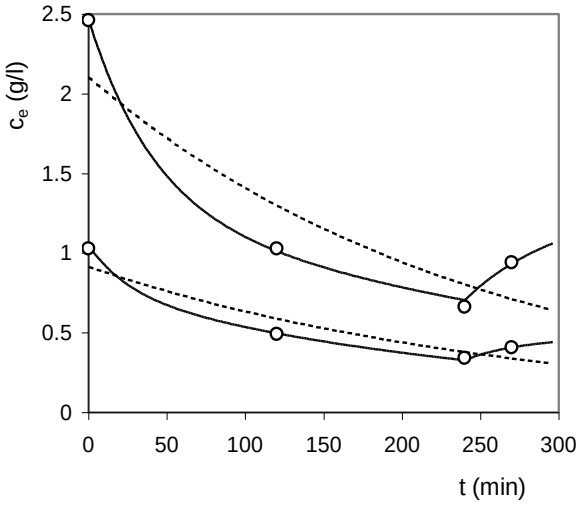

Fig. 2. Experimental and calculated urea concentrations (solid line: two-compartment model; dashed line: single-pool model).

The overall quality of fit can be well appreciated from the scatter plots shown in Figure 3, where the calculated urea concentrations are plotted against the experimental ones. Data points relative to the two-compartment model are closely clustered around the bisection line, with an average percent error of 3.4%. For the single-pool model the average error is 14.8%, and apparent systematic deviations occur. In particular, at concentrations corresponding to predialysis urea levels (roughly c_e > 1 g/l) model responses are systematically lower than experimental data. For c_e < 1 g/l two clusters are observed: one above the bisection line ($c_e^{calc} > c_e^{exp}$), corresponding to data at 120 and 240 min, and one below ($c_e^{calc} < c_e^{exp}$), indicating underestimation of urea rebound.

Evaluation of dialysis efficiency by eqn. (4) leads to the results reported in Table 3. Values so obtained (51.7% ± 5.8) are significantly lower than predictions from the single-pool model, yielding an URR of 59.2% ± 5.1. Calculation of URR by substitution of measured urea levels in eqn. (6) gives 67.1% ± 5.3, which is appreciably higher than the former ones.

Table 3. Dialysis efficiency as determined from URRs (URR* is calculated by using measured concentrations)

Patient	URR (eqn. 4)	URR (eqn. 6)	URR* (eqn. 6)
1	57.2 ± 3.0	58.6 ± 3.6	66.4 ± 3.4
2	51.5 ± 2.8	59.6 ± 2.5	70.2 ± 2.0
3	58.0 ± 4.3	66.2 ± 3.2	74.4 ± 2.6
4	55.1 ± 3.1	65.0 ± 2.9	72.8 ± 2.3
5	57.7 ± 2.7	56.3 ± 2.3	64.5 ± 2.6
6	51.2 ± 1.7	56.9 ± 0.9	63.7 ± 1.0
7	43.8 ± 1.9	60.7 ± 3.5	68.3 ± 2.7
8	43.4 ± 2.6	48.7 ± 1.8	56.5 ± 2.5
9	47.4 ± 4.2	59.8 ± 5.0	66.9 ± 4.6
-	51.7 ± 5.8	59.2 ± 5.1	67.1 ± 5.3

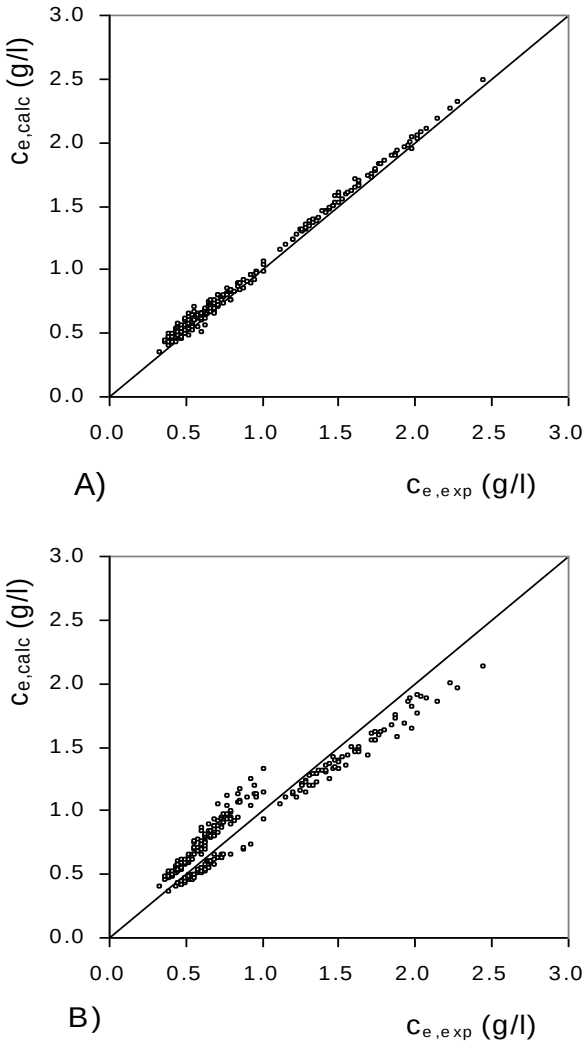

Fig. 3. Experimental and calculated urea concentrations (A: two-compartment model; B: single-pool model).

Overestimation of dialysis efficiency, when using eqn. (6), is to be connected to the fact that at the end of dialysis the total amount of urea is much higher than that determined considering the extracellular concentration only. In fact, due to compartment heterogeneity, when dialysis is stopped high urea levels are still present in the intracellular space. In addition, this compartment is larger than the extracellular one, which further contributes to increasing the final amount of urea.

4 CONCLUSIONS

The kinetic model developed in this study provides an accurate description of the urea concentration decay during dialysis as well as of postdialysis urea rebound. Large differences have been found in dialysis efficiency estimates by this and the single-pool model. According to the data presented here, overestimations of up to 20% may result in the calculated URRs.

It seems interesting to note that, once the patient-related parameters – namely, AK_c and γ – have been determined, the model can be used as a predictive tool to estimate both intra- and inter-dialytic changes in total body urea. This could be helpful for assessing optimal criteria of dialysis prescription.

ACKNOWLEDGEMENTS

The Authors are grateful to S. Petrucci (Nephrology and Dialysis Unit, Complesso Integrato Columbus, Roma, Italy) for his valuable technical contribution, and to Prof. G. Splendiani (Department of Nephrology, Tor Vergata University, Roma, Italy) for his support and helpful discussion.

We sincerely thank the patients who volunteered for this study.

REFERENCES

1. R.M. Hakim, J. Breyer, N. Ismail and G. Schulman, Effects of dose of dialysis on morbidity and mortality, *Am. J. Kidney Dis.* 23 (1994) 661-669.
2. R.M. Lindsay and J. Sternby, Future directions in dialysis quantification, *Semin. Dial.* 14 (2001) 300-307.
3. D. Schneditz and J.T. Daugirdas, Compartment effects in hemodialysis, *Semin. Dial.* 14 (2001) 271-277.
4. F. Maduell, J. Garcia-Valdecasas, H. Garcia, J. Hdez-Jaras, F. Sigüenza, C. del Pozo and E. Garrigos, Validation of different methods to calculate Kt/V considering postdialysis rebound, *Nephrol. Dial. Transplant.* 12 (1997) 1928-1933.
5. D.E. Matthews and R.S. Downey, Measurement of urea kinetics in humans: a validation of stable isotope tracer methods, *Am. J. Physiol.* 246 (1984) 519-527.
6. S.W. Smye, J.H.C. Evans, E. Will and J.T. Brocklebank, Pediatric haemodialysis: estimation of treatment efficiency in the presence uf urea rebound, *Clin. Phys. Physiol. Meas.* 13 (1992) 51-62.