Simulating the Effect of Exercise on Urea Clearance in Hemodialysis

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Abstract. A two-compartment model of urea kinetics during hemodialysis is used to predict the effect of exercise on hemodialysis dose. It is assumed that the two compartments represent tissues that are perfused by low and high blood flows (initially 1.1 L/min and 3.8 L/min). The effect of changing the distribution of flows between the compartments, emulating the effect of exercise, is simulated using the model equations for a range of dialyzer clearances. Compartmental volumes are assumed constant (33.4 L and 8.6 L for low- and high-flow compartments, respectively). The analysis identifies muscle perfusion as a rate-limiting factor during the later stages of hemodialysis and illustrates the benefit of exercise during this phase in increasing dialysis efficiency. The model suggests that the postdialysis rebound in the blood urea concentration is eliminated by increasing flow to the low-flow compartment from 1.1 L/min to 7.1 L/min and sustaining this for at least 30 min of a 150-min dialysis session, independent of the dialyzer clearance. Additional exercise will not increase the dialysis dose. Experimental studies are required to confirm the analysis. (J Am Soc Nephrol 9: 128–132, 1998)

In practice, there are limited means of increasing the dialysis dose. Dialyzers have become more efficient, and increasing blood flows help increase clearance. Extending dialysis times is less acceptable to patients and is costly. Urea kinetic modeling is firmly established as an approach to the problem of estimating hemodialysis adequacy. However, the importance of developing and applying a kinetic model lies not only in the determination of dialysis dose, but also in providing insights to the underlying solute transport mechanisms. These insights may be expected to inform novel dialysis strategies and help to optimize clinical procedures.

Urea kinetic models were first developed by Dedrick and Bischoff (1). Gotch and Sargent subsequently applied a single pool model to a clinical population when analyzing the results of the National Cooperative Dialysis Study (2). This analysis used a variable volume single pool model of urea distribution and expressed hemodialysis dose as $Kt/V$, where $K$ and $t$ denote dialyzer clearance and treatment time, respectively, and $V$ denotes the national single pool urea distribution volume.

Models of urea kinetics were subsequently extended to explain the postdialysis urea rebound (3), which increases with relative clearance $K/V$. In a two-compartment model, the urea is assumed to be distributed in a two well-mixed compartment, initially identified as intra- and extracellular compartments (3), between which urea transport occurs by diffusion. Schneditz et al. (4,5) have since shown that variations in regional blood flow could result in an effective multicompartamental distribution and on this basis account for the postdialysis urea rebound.

In this approach, the two-compartment distribution arises from two tissue compartments perfused by either low or high blood flows, and the mixing of blood with different urea concentrations between these compartments accounts for a major part of the postdialysis rebound.

This article uses the flow model of urea kinetics to assess the likely effect of changing blood flow on dialysis efficiency and considers the implication of these findings for dialysis strategies. In this analysis, the solute considered is urea, although a similar approach may be developed for other solutes.

Model Development

The basic model (4) comprises a high-flow compartment (small organs, lungs, blood, heart, brain, and portal system; references 4 and 6) in parallel with a low-flow compartment (bone, muscle, skin, and adipose tissue; references 4 and 6) (see Figure 1). If $V_L$ and $C_L$ denote the urea distribution volume and concentration in the low-flow compartment and $V_H$ and $C_H$ denote corresponding parameters in the high-flow compartments, assuming that diffusion of urea between tissue and blood is rapid gives:

$$\frac{d(V_L C_L)}{dt} = (C_s - C_L)Q_L + C_L \frac{dV_L}{dt} \hspace{1cm} (1)$$

$$\frac{d(V_H C_H)}{dt} = (C_s - C_H)Q_H + C_H \frac{dV_H}{dt} \hspace{1cm} (2)$$

where $Q_L$ and $Q_H$ denote the flow to the low- and high-flow compartments, respectively, $C_s$ is the urea concentration in the arterial
Figure 1. Two-compartment urea kinetic model used (from Schneditz et al. [4]) for simulation of effects of exercise. Notation as in text.

Blood, and urea generation and ultrafiltration have been neglected. By conservation of mass, the concentration of urea in the mixed venous pool is:

\[ C_v = u C_H + (1 - u) C_L \]

where \( u = \frac{Q_H}{Q_S} \) and \( Q_S \) denotes the systemic flow \( (Q_H + Q_L) \). Neglecting any delays in mixing due to the finite time required for blood to pass along the different vessels, the venous blood mixes in the heart with blood from the access and dialysis venous line giving:

\[ Q_c C_a = Q_S C_s + Q_L C_L + Q_H C_H \]

where \( Q_c, Q_s, \) and \( Q_H \) represent the cardiac output, fistula bypass, and dialyzer blood flows, respectively, and \( C_H \) is the concentration of urea at the dialyzer outlet. Neglecting access recirculation, if the dialyzer urea clearance is \( K_d \), then:

\[ C_s = a C_H + b C_L \]

(3)

where \( a = Q_H/(Q_S + K_d) \) and \( b = Q_L/(Q_S + K_d) \). Assuming that the various blood flows and \( K_d \) are constant throughout the dialysis, equations 1 through 3 give (7):

\[ C_H = A e^{-\lambda_H t} + B e^{-\lambda_L t} \]  

(4)

\[ C_L = C e^{-\lambda_L t} + D e^{-\lambda_H t} \]  

(5)

where \( A, B, C, D, \lambda_H, \) and \( \lambda_L \) are constants derived from the initial condition \( C_H(0) = C_L(0) = 1 \) and given in detail in Appendix 1. The urea concentration is expressed as a fraction of the initial concentration, and the compartmental volumes are assumed to be constant. The mass (\( m \)) of urea removed during dialysis is given by:

\[ m = (V_H + V_L) - (V_H C_H(T) + V_L C_L(T)) \]  

(6)

with the postdialysis equilibrium urea concentration \( C_e \) given by:

\[ C_e = 1 - \frac{m}{(V_H + V_L)} \]  

(7)

Because the compartmental volumes are assumed to be constant \( (V_H = 8.6 \text{ L} \) and \( V_L = 33.4 \text{ L} \), respectively; references 4 and 6) and urea generation has been neglected, the true dialysis dose is given by \( K t/(V_H + V_L) \), and the apparent dose given by the single-compartment model is \( \log_a (1/C_H(T)) \). The difference (\( D \)) between the apparent and actual dialysis doses is therefore given by:

\[ D = \log \left[ \frac{1.0}{C_H(T)} \right] - \frac{K t}{(V_H + V_L)} \]  

(8)

The postdialysis percentage rebound in urea concentration is defined as:

\[ R = 100 \left( \frac{C_e - C_H(T)}{C_e} \right) \]  

(9)

The effect of changes in the distribution of blood flow on the rebound and difference between the apparent and actual dialysis doses
may be simulated by varying $Q_L$ and $Q_H$ during the treatment. It is assumed that exercise produces an increase in the perfusion rate $Q_L$ of the low-flow compartment (initially assumed to be 1.1 L/min; references 4 and 6) due to changes in cardiac output (8), whereas $Q_H$ remains constant (3.8 L/min) (6). Given that exercise may produce up to a 10-fold increase in the muscle perfusion rate (8), but that this increase may not be achieved in patients with renal failure, it is assumed that $Q_L$ increases smoothly from 1.1 to 7.1 L/min over a 20- to 30-min period and then remains constant. This is consistent with regular periods of exercise of, for example, 10 min duration (9) interspersed with a short recovery period (several minutes), during which the high flow to the muscle compartment is sustained. This analysis also assumes that the access blood flow remains constant throughout the dialysis session and is independent of exercise.

The effect of this exercise regimen will depend on the time into dialysis when the increase in $Q_L$ occurs. For the purpose of the calculation, this time is defined by $t_T$, the midpoint of the 20-min period of increasing flow. $f$ therefore represents the fractional time into dialysis at which this exercise occurs. $f = 0$ suggests that the patient began exercising before starting dialysis. If $f > 1$, the first exercise period occurred close to the end of, or after, dialysis and will have little or no effect on the urea kinetics. The flow $Q_L$ at time $t$ is represented mathematically by:

$$Q_L = 1.1 + 6.0 \left[ \frac{e^{(20(t-f)/T)}}{1 + e^{(20(t-f)/T)}} \right],$$

and the dependence of $Q_L$ on $f$ and $t$ is shown diagrammatically in Figure 2 for $0 < t < 150$ and $0.5 < f < 1.5$.

In this case, the solutions to equations 4 and 5 no longer apply, and a numerical solution is required. The effect of changes in the distribution of blood flow and the dialyzer clearance ($K$) on the rebound ($R$) and difference ($D$) between the apparent and actual dialysis doses is simulated using equations 1 through 3 and 8 through 10 for $0.5 < f < 1.5$ and $0.15 < K < 0.35$ L/min and $T = 150$ min. Numerical solutions to the equations were obtained using Mathematica (version 2.2, Wolfram Research, Inc., Champaign, IL) on a PC platform (130 MHz Pentium [Intel], Ebonex, Ltd., London, United Kingdom).

**Results**

The results of the simulation are illustrated in Figures 3 and 4, which show the effect of variations in $f$ and $K$ on percentage rebound ($R$) and the difference ($D$) between the true and actual dialysis dose. Figures 5 and 6 demonstrate the variation in
and the clearance from skeletal muscle, skin, and bone occurs more slowly. The time dependence of blood urea concentration during this phase (see Figures 5 and 6) reflects the dialyzer clearance rate, because the time required to clear urea through the dialyzer is much longer than the times associated with clearance from the high flow rate tissues. Subsequently, the contribution of urea from the well-perfused tissues to the blood level of urea becomes negligible, and the dominant factor is the transport of urea from the poorly perfused skeletal muscle, skin, bone, and fat, and subsequent urea clearance through the dialyzer. The rate-limiting step becomes the perfusion of skeletal muscle, skin, and bone. If muscle blood flow remains constant during this stage, and it is assumed that clearance through the dialyzer is relatively rapid, then the rate of decrease in blood urea concentration reflects the muscle perfusion rate. After dialysis, the rebound in urea concentration is due to blood from high flow tissues with a relatively low urea concentration, mixing with that from skeletal muscle, bone, and skin, which have a higher urea concentration. Exercise during hemodialysis results in an increase in the rate of skeletal muscle, bone, and skin compartment urea clearance by a factor of up to 6 and a reduction of the concentration gradient between the two compartments. The arterial urea concentration rises after onset of exercise (compare Figures 5 and 6 for t > 60 min), reflecting the increase in urea transport from the low-flow compartment.

The analysis emphasizes that an improvement in dialysis clearance is likely to be achieved by improving muscle perfusion during the later stages of dialysis, rather than simply increasing dialyzer clearance. In this model, there is a theoretical limit beyond which no further increase in dialysis dose is achieved. The dose of dialysis may thus be increased by clinical procedures designed to optimize tissue blood flow during the application of any particular dialyzer and access flow rate. There may be pharmacological means of preparing and sustaining tissue perfusion to take advantage of the relatively narrow range of convenient and cost-effective dialyzer clearances.

The study gives a theoretical basis for developing and interpreting further experimental studies designed to study the effect of exercise on dialysis dose. It also suggests a basis for optimizing these regimens to ensure that the maximum dose of dialysis is delivered with minimum patient effort.

**Appendix 1**

In the main text, the solutions of the model equations 1 and 2 under conditions of constant volume and flow are given by equations 4 and 5 (see references 4 and 7), with the constants defined by:

\[
A = \frac{1 - \alpha_2}{\alpha_1 - \alpha_2}; \\
B = \frac{\alpha_1 - 1}{\alpha_1 - \alpha_2}; \\
C = \alpha_1 A; \\
D = \alpha_2 B
\]

\[
\lambda = \frac{q \pm \sqrt{q^2 - 4pr}}{2p}
\]

\[
\alpha_1 = \frac{a}{[1 - b - (V_1 \lambda_1 / Q_d)]}; \\
\alpha_2 = \frac{a}{[1 - b - (V_1 \lambda_2 / Q_d)]}
\]
and \( p = V_H \cdot V_L \); \( q = V_H \cdot Q_L \cdot (1 - b) + (1 - a) \cdot V_L \cdot Q_H \); \( r = Q_H \cdot Q_L \cdot (1 - a - b) \). Urea concentrations have been expressed as a fraction of the initial concentration.

**References**