Consequences of more physiological flow distribution models on the \(Kt/V\) concept

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Introduction

Today there are a variety of renal replacement therapies for the increasing number of humans with severe renal insufficiency. There have been numerous technical and medical advancements over the years that have improved the treatment quality considerably, but still there are high morbidity and mortality rates in this population. The importance of quantifying the dialysis treatment has become apparent during the last decade and has resulted in attempts to increase the dialysis dose. Still, the equivalent renal function obtained with haemodialysis (HD) as well as with peritoneal dialysis (PD) is only a fraction of normal values. Normally, the kidneys process 180 l of primary urine each day in order to maintain a constant biochemical environment for our cells. Moreover, since the transglomerular passage is largely unrestricted even for larger solutes (Stokes–Einstein radius < 20 Å), this implies a clearance for most solutes of 125 ml/min (1260 l/week or a weekly \(Kt/V\) of > 30). Hence, ‘adequate dialysis’ can be expressed in terms of a fractional clearance such as weekly \(Kt/V\) for urea, which is often cited to be > 2 for PD and > 3.6 for HD. Thus, the dialysis clearance for urea is one order of magnitude smaller than that of normal kidneys, and even more importantly the clearance values drop dramatically with increasing molecular weight. Moreover, the normal renal function is continuous whereas several dialysis modalities are of an intermittent nature. It has been found, however, that the fractional clearance \((Kt/V)\) for urea reflects the quality of dialysis \([1–4]\), and the same is probably true also for the clearance of various other solutes, e.g. creatinine.

When the \(Kt/V\) concept was introduced \([4]\), a single compartment analysis was used. In such a model, the \(Kt\) product (where \(K\) is clearance and \(t\) is time) will give the total amount of solute removed. Expressing \(Kt\) as a fraction of the volume of distribution \((V)\) gives the fractional clearance. However, the body has several different compartments with quite variable blood flows \([5]\), which has important implications for dialysis \([6,7]\). Recently, various multi-compartment models have been successful in explaining urea rebound after HD \([8–13]\). In a previous attempt to visualize some consequences of applying the one-compartment \(Kt/V\) concept, an extreme case of blood flow heterogeneity was used \([14]\). In the present report, a more realistic model is used, and it will become evident that the conclusions are basically the same.

Physiological considerations regarding dialysis

Dialysis removes mainly water-soluble small molecules which are distributed in the body fluid compartments. Of the total body water (TBW), two-thirds is in the cells (ICV) and one-third constitutes the extracellular compartment (ECV). During dialysis, it is only the plasma fraction of the latter compartment that equilibrates with the dialysis fluid. Therefore, the removal of solutes is totally dependent on the diffusion to plasma from the other compartments. Moreover, whereas some solutes such as urea are distributed in the TBW, some other solutes may reside mainly extracellularly (e.g. sodium) or intracellularly (e.g. potassium).

From a theoretical point of view, there are several factors of greater or lesser importance affecting the passage of solutes from the peripheral compartments to plasma: (i) restriction across the cell membrane; (ii) interstitial diffusion and concentration gradients; (iii) protein binding; (iv) passage across the capillary wall; (v) the number of capillaries perfused; and (vi) the regional blood flow. At least for urea, the cell membranes do not seem to offer any major hindrance to diffusion \([15]\). The second factor of interstitial concentration gradients is hardly a problem for urea in normally hydrated tissue. It may, however, be important for other solutes, particularly in the presence of oedema. Certain solutes are poorly removable by dialysis due to protein binding, and such protein–solute complexes are also removed slowly from the interstitium. The capillary wall offers no restriction whatsoever for small solutes like urea, but will markedly retard the diffusion of larger molecules \([16–18]\) such as \(\beta\)-microglobulin. Finally, the capillary density and the
The present multi-compartment model

The present model is a modification of that presented in a previous paper [14]. Let us assume that the 'muscles' can be treated as two compartments; one (A) with a distribution volume of 9 l, weighing 15 kg, with a blood flow of 150 ml/min (=1 ml/min/100 g) and another (B) larger muscle compartment (21 l or 35 kg) with a blood flow of 2050 ml/min (=5.9 ml/min/100 g). All other organs (e.g. the brain, liver, intestine, heart, kidneys, etc.) are part of a third compartment (V = 9 kg, W = 15 kg) with a blood flow of 2800 ml/min. The blood compartment contains 5 l and the total cardiac output would thus be 51/min. All compartments are assumed to have constant volumes. Initially, all three tissue compartments and blood have identical concentrations of the solute X with the value of 1 arbitrary unit. X is generated in all tissue compartments at the same rate (XGR) per gram of tissue, reaching a total XGR of 0.009 arbitrary units per min. There is no renal function. The body can be dialysed by replacing X-containing blood with blood free from X at a given flow (=clearance) for a certain period of time. The venous blood is assumed to be completely equilibrated with the surrounding tissues (probably true for urea but not for larger solutes) and to reach the same concentration as in each of the three well-mixed tissue compartments. The concentrations of the plasma and the tissue compartments are monitored over time as dialysis starts. Moreover, the amount of solute X removed is determined as a function of time for different modes of dialysis. Hereby, it is possible to construct relationships between removed mass and Kt/V for X for different forms of dialysis treatment.

Calculations

The concentration C1 of solute X in a tissue compartment 1 at time t is:

\[ C_1(t) = C_1(t - \Delta t) + \frac{\Delta t \left[ Q_{\text{in}}(C_1(t - \Delta t)) + XGR_1 \right]}{V_1} \]

where \( V_1 \) is the volume of distribution (l) which is assumed to be constant. The blood flow to the tissue is denoted \( Q_1 \) (1/min) and equals that from the tissue. The XGR1 is the generation rate (units/min) of solute X, and \( C_1 \) is the blood concentration (units/l). Moreover, the blood concentration \( C_h \) at time t is given by:

\[ C_h(t) = C_h(t - \Delta t) + \frac{\Delta t \left[ \sum_{n=1,2,3} \left[ C_n(t - \Delta t) - C_h(t - \Delta t)Q_{\text{out}} \right] - C_h(t)Q_{\text{out}} \right]}{V_h} \]

where \( Q_{\text{out}} \) is the clearance of solute u from blood. The removed amount of solute (m) is:

\[ m = \int_0^T \left( Q_{\text{out}}(t) - C_h(t) \right)dt \]

where \( Q_{\text{out}} \) and \( C_h \) change with time.

For each time t of dialysis, different Kt/V values can be simulated by altering the \( Q_{\text{out}} \) which is equivalent to the clearance (K) of the dialyser. The calculations are thus based on mass balance and the effects are simulated minute by minute for 1 week of treatment using various dialysis modalities. In a homogenous single compartment model, the removed mass, m, will depend solely on the Kt/V product and not on treatment time, t, or the frequency of dialysis.

Results

Temporal changes of the concentration of solute X in the three tissue compartments and in plasma

Figure 1 illustrates how the concentration changes in the compartments during and after HD for 4 h with an average clearance of 180 ml/min (treatment Kt/V = 1.1). Note that 1 h after HD most of the 'urea rebound' seem to be completed if one looks at the blood compartment. However, the concentration of solute X in the slowly perfused muscle compartment A is still 10% greater than that of plasma, and complete equilibration is actually not seen within the 8 h post-dialysis period even though the differences are extremely small 3 h after HD.

Overestimates of urea and creatinine generation rates

One consequence of a slowly equilibrating compartment is that the generation rates calculated from blood samples taken after HD and immediately before the next dialysis overestimate the 'true' values. This probably explains the well-known dilemma of why different equations for calculations of protein catabolic rate (PCR) from urea generation rate (UGR) are needed depending on whether the patient is treated with HD or PD [23]. In order to obtain the same PCR value, the HD patient needs 15% higher UGR [23]. Using the present multi-compartment analysis, this difference can be explained by the combined effects of the rapid
A new multi-compartment model for the Kt/V concept

Fig. 1. Concentration of solute X in arbitrary units in three tissue compartments and plasma during and after 4 h of haemodialysis with a clearance of 180 ml/min, i.e. with a Kt/V of 1.1.

urea rebound phenomenon and a second slow equilibration of certain muscle regions. Note that if one tries to correct for urea rebound by taking a post-dialysis blood sample 15 min after the treatment, the PCR equations developed for HD are no longer valid since they will underestimate 'true' PCR. Perhaps one should use the PCR equations described for the PD population instead, e.g. the relationship described by Bergström et al. [23].

The impact of treatment time on the removed mass of solute

The most important consequence of a multi-compartment model is probably that the treatment time will have marked effects on the removed mass for any given single compartment Kt/V value. This is illustrated in Figure 2 for several different treatment modalities. The dotted lines illustrate the Kt/V values needed to remove the same amount of solutes. Thus, a weekly Kt/V of 1.7 for continuous treatment (24 h/day 7 days/week) is comparable with intermittent HD (4 h 3 days/week) with a Kt/V of 2.4. Hence, the dialysis paradox of why two completely different weekly Kt/V values are needed for adequate PD and HD treatments seems to be due to the multi-compartment nature of the human body.

The impact of the frequency of dialysis on the removed mass of solute

Figure 3 illustrates that giving daily HD reduces the weekly Kt/V value needed to remove a given amount of solutes to 1.9 compared with 2.4 for three HD per week or 2.7 for two HD per week. Moreover, daily dialysis requires a lower ultrafiltration rate which probably will elicit less cardiopulmonary reflexes which would, if anything, enhance the effect of frequency.

Discussion

The principal role of the normal kidney is to maintain a constant biochemical environment for the cells. Therefore, continuous or daily dialysis modalities are physiologically superior to intermittent renal replacement therapies. Moreover, the present simplistic multi-compartment model demonstrates that for a given Kt/V value more solutes are removed if the dialysis is more frequent. It is also apparent that more solutes are removed if the treatment time is increased despite constant Kt/V products. All these effects are due to the fact that single pool analysis of the changes in blood composition are expressed in terms of a Kt/V value. A more direct approach for quantifying dialysis is to measure the amounts of solutes removed and present in the dialysate. Such measurements [24] seem to correspond well with the results presented in this study. Note that the mass balance calculations are valid for the multi-compartment model during the period studied. In metabolically stable patients, the amount of urea removed will always equal the urea generated. If the dialysis is less effective, the blood concentrations will increase, food intake will often decrease and metabolic changes may occur, resulting in a new balance point where input equals output. This will occur eventually in the model as well, but with the solute generation rate chosen it will take more than 1 week to reach a new semi-steady state. Thus it is possible to illustrate the consequences of dialysis in a multi-compartment model with the simple term
Fig. 2. The effect of treatment time on the removed mass. The curves represent continuous dialysis, daily dialysis 12 h/day, and intermittent dialysis 8, 4 and 1 h three times per week. The hatched lines illustrate the various Kt/V values required to remove the same amount of \( X \).

Fig. 3. The effect of frequency of dialysis on the removed mass. The curves represent continuous dialysis, daily dialysis each of 4 h and intermittent 4 h dialysis once or twice per week. The hatched lines illustrate the various Kt/V values required to remove the same amount of \( X \).

‘removed mass’ instead of ‘equilibrated semi-steady state concentrations’.

In the present model, the solute concentration of the venous blood returning from an organ is assumed to be in complete equilibration with the interstitial and intracellular compartments of that organ. While that probably is correct for solutes such as urea, it is not likely for other solutes. Take, for example, \( \beta_2 \)-microglobulin, a well-known uraemic toxin, where there is significant restriction for diffusion across the capillary walls [25] and the compartmental effects are thus most probably exaggerated. Therefore, the advantages of using continuous or daily dialysis in terms of solute removal will be even more apparent for solutes other than urea. More ‘intense’ dialysis will for several reasons result in a proportionally greater removal of urea than of larger solutes (e.g. creatinine and others). At present, it is an open question as to whether the severity of the uraemic syndrome is best described by the clearance of urea, creatinine or some other molecule. The case for urea and/or creatinine as important parameters is strengthened by the fact that the recommended minimum value for dialysis corresponds to a glomerular filtration rate (GFR) of \(~6\) ml/min/
1.73 m². At this level of dialysis, the clearance of 'middle molecules' is closer to 1 ml/min. For comparison, the pre-dialytic patient with a GFR of ~5 (for almost all solutes, see above) is considered to be highly uraemic and ready for dialysis. Thus, the concept of clearance (or Kt/V) for urea/creatinine seems to reflect the uraemic syndrome both before and during dialysis.

To conclude, adopting more physiological multi-compartment models offers explanations to several apparent dialysis paradoxes between PD and HD. In particular, several advantages of using daily or continuous instead of intermittent dialysis are evident when the effects of blood flow distribution and cardiopulmonary reflexes are considered. A great challenge for the next few years is to design studies to test the various predictions of the multi-compartment models. It is also important to express the compartment effects model.

24. Chandran PKG. Kt/V estimates of hemodialysis (HD) using concentration changes overestimate the effect of HD compared to CAPD. J Am Soc Nephrol 1994; 5: 511

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References