Mathematical Concept of Dialysis Unphysiology

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Although the unphysiology of the intermittently applied dialysis treatment was a concern of the dialysis pioneers, the development of any mathematical theory of treatment unphysiology and its quantification was not attempted until the end of the 1980s. This paper suggests that the conventional urea kinetic modeling (UKM) be complemented with a new parameter, the time-averaged deviation (TAD). TAD is the mean plasma urea concentration fluctuation around its mean value (time-averaged concentration, TAC). The value of TAD increases with a decreasing number of dialysis treatments per week, that is, with increasing dialysis unphysiology. Thus it can be used to quantify this until now only intuitively assessed treatment parameter. Status of a patient on any given treatment schedule can be characterized by a point on the TAC/TAD plot. Sensitivity analysis performed using the TAC/TAD plot offers insight into the influence of different patient- and treatment-related parameters on the point location and thus enables both retrospective as well as prospective assessment of different treatment schedules. Clinical correlates of TAD will have to be found and studied to establish the importance of the treatment schedule unphysiology for the overall treatment outcome.

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Key words

Dialysis unphysiology, time-averaged concentration, time-averaged deviation, urea kinetics

Introduction

Ever since the inception of the chronic hemodialysis program there have been numerous attempts to quantify the prescription of dialysis treatment and to measure the actual delivered dose. In fact, most of the first attempts were made in the United States: the dialysis index (DI), developed by Babb *et al.* (1), and urea kinetic modeling (UKM), introduced by Sargent and Gotch (2), which in its simplified form of Kt/V remains the most widely applied approach.

Because of the rather low efficiency of the early dialysis devices, efforts of the early dialysis researchers were aimed at defining dialysis adequacy in terms of its efficiency. Moreover, target values of those criteria were established mostly for one specific treatment schedule, usually three hemodialysis (HD) sessions per week. Inappropriate use of such criteria and target values for a different treatment schedule [known dilemma caused by comparing weekly Kt/V values of thrice-weekly HD with weekly Kt/V in peritoneal dialysis (PD)] led to the development of alternative theoretical approaches, such as the solute removal index (3) and equivalent clearance (4). These methods enabled a theoretically correct comparison of different treatment schedules in terms of their efficiency and gave birth to the concept of incremental dialysis (5). Yet experienced dialysis practitioners occasionally note that even an increase of the equivalent clearance, of say thrice-weekly HD, by a value equal to a decrease in residual renal function does not fully compensate for this loss of function of a natural kidney. This means that something is still being neglected in our consideration on treatment strategy. This unknown and so far unappreciated parameter may be the unphysiology of the intermittent renal replacement therapy.

Similarly, assuming a constant and equal production of waste metabolites, such as urea, in an individual on two different treatment schedules (twice- and thrice-weekly HD), it can be shown that the same time-averaged concentration (TAC) can be obtained on both schedules (Figure 1A). Even if we want to reach the same peak plasma urea concentration within the whole week, an increase in dialysis time of 1.5 hours on the twice-weekly schedule will allow this (Figure 1B). Assuming further that the patient is on both schedules in a dynamic steady state, it is obvious that the same weekly amount of urea will be excreted in both the twice- and thrice-weekly HD schedules. Yet clinical experience indicates that the dialysis schedule with three HD sessions per week is superior to the twice-weekly schedule. Again, there is just one difference in this hypothetical patient: the magnitude of fluctuation of the plasma waste products level, which, in fact, is a sign of "unphysiology" of the given treatment schedule.

Kjellstrand *et al*. (6) were the first to address the issue of possibly negative effects of dialysis unphysiology. However, their idea remained unnoticed for nearly the next two decades. With the increasing variety of dialysis schedules, both in HD (HD every other day, daily HD) and in PD (continuous ambulatory PD) that we witness today, it may be useful to look closer at the unphysiology issue. To make the concept of dialysis unphysiology practically usable for comparison of different schedules and/or optimization of the treatment schedule, the "unphysiology" needs to be mathematically formalized and possibly built into an existing method of dialysis adequacy assessment.

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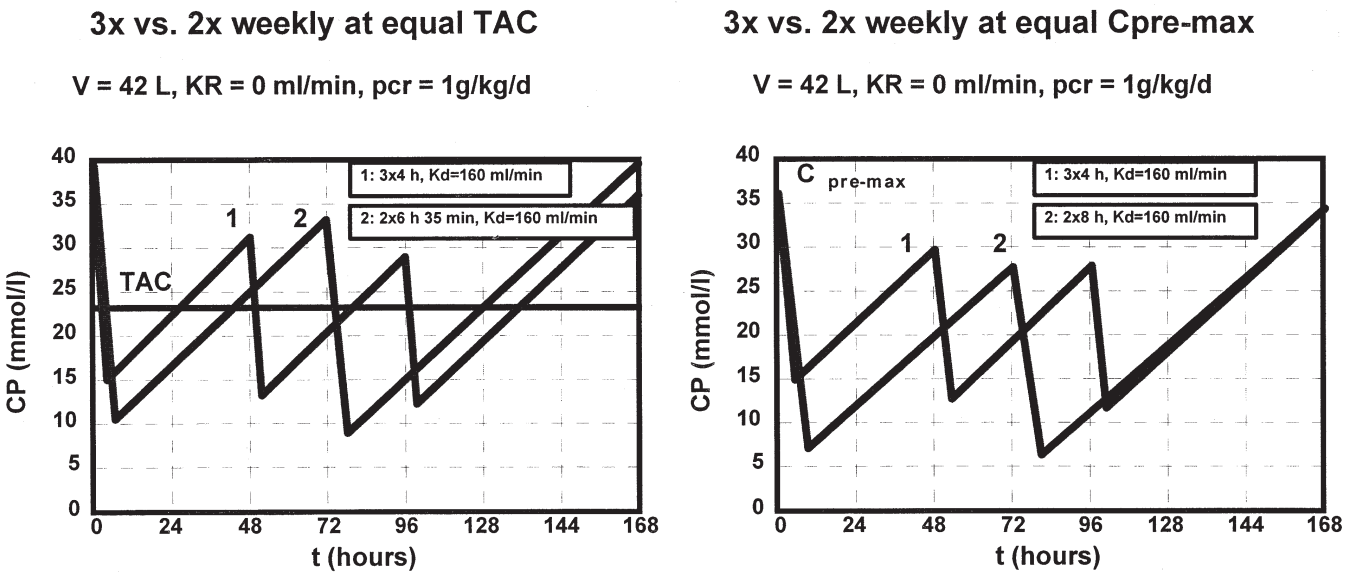

FIGURE 1 Plasma urea profile on thrice- (curve 1) and twice- (curve 2) weekly dialysis with identical TAC (A) (left) and identical maximal predialysis level (B). Note: $C_{pre\text{-}max}$ is the maximal predialysis urea level over the whole week cycle, that is, the predialysis level after the longest interdialytic period. V = urea volume of distribution; KR = residual renal clearance; pcr = protein catabolic rate.

Classical setup of dialysis schedule and strategy

Any theoretical approach to setting up a dialysis treatment strategy works with three parameters: clearance (*Kd*), length of dialysis session or treatment time (*Td*), and frequency of dialysis, that is, number and distribution of dialysis sessions in a week (*n*). To determine three function parameters in any system necessitates three independent equations or criteria conditions. However, both dialysis adequacy criteria mentioned in the Introduction, that is, DI and UKM, dispose of only one equation, defining the desirable value of DI or Kt/V. Thus in the process of setting up the dialysis schedule, two of the three parameters (*Kd*, *Td*, *n*) have to be arbitrarily chosen. Traditionally, such arbitrary choice was applied for dialysis time and number of dialyses per week (*n*). Dialysis time was usually defined to suit organizational needs of a given dialysis center. More rational has been the choice of dialysis frequency; patients with nonzero residual renal clearance (KR) were dialyzed twice weekly, and when they finally became anuric, they were transferred to a thrice-weekly schedule. (This latter step, in fact, reflected the intuitive perception of the overall treatment quality, itself including the issue of treatment physiology, although it was usually explained merely by the need to increase efficiency of dialysis without making each session unacceptably long.)

Quantification of the treatment schedule unphysiology

To quantify the dialysis treatment schedule unphysiology, we use an analog to a quality control criterion often used in engineering: time integral of the deviation of the controlled variable from its desired steady-state value. In the case of dialysis treatment, which is also a type of a control process, the desired steady-state value corresponds to TAC, and the integral of the plasma concentration profile with the TAC taken as the zero level may be interpreted as the time integral of the deviation of the controlled variable. The newly introduced parameter, the so-called time-averaged deviation (TAD), is thus the mean value of fluctuation of the plasma concentration around the TAC value (7). Mathematically, both TAC and TAD are defined in very much the same way as elucidated in Figure 2. Under otherwise comparable conditions, fluctuation of the plasma concentration is always higher in less frequent or irregular schedules as compared to more frequent or regular schedules. Thus the TAD can be used to quantify the unphysiology of a given treatment schedule.

Compared to the one-dimensional approach of conventional UKM, the TAC/TAD approach is two-dimensional. Instead of characterizing the treatment schedule by a single number (be it TAC or the Kt/V value), it can now be characterized by a point in a two-dimensional plot TAC/TAD (Figure 3).

The strength of this new approach becomes obvious when we manipulate different treatment- and patient-related parameters and evaluate the impact of these manipulations on the outcome variables, that is, TAC and TAD. As can be seen from Figure 3, *Kd* and *Td* as treatment parameters influence only the TAC value and have practically no impact on treatment unphysiology, as assessed by the TAD. Contrary to this, any change in patient parameters pcr (protein catabolic rate normalized per kilogram of body weight) and/or residual renal clearance (KR) influence both TAC and TAD. From among the treatment-related parameters, only frequency of dialysis may bring about a significant change in the TAD

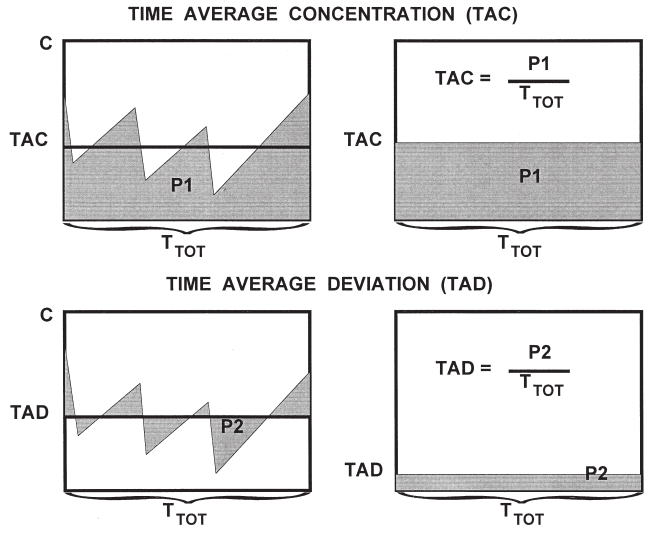

FIGURE 2 Definition of TAC and TAD. Both TAC and TAD are defined as standard time-averaged values from the weekly urea concentration profile, TAC as the mean value of the profile and TAD as the mean fluctuation of the concentration around its TAC value.

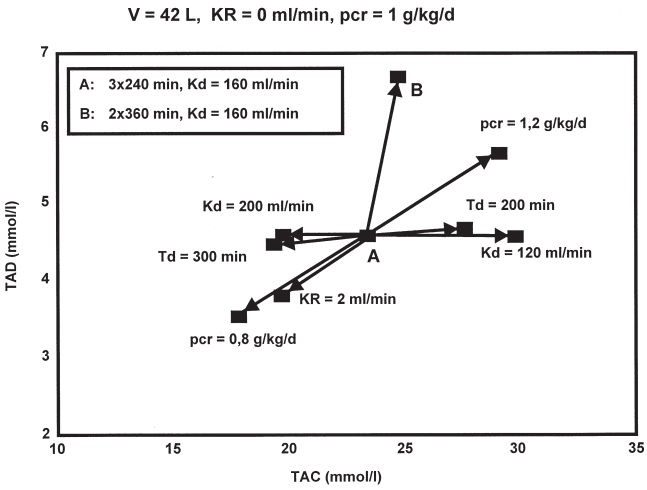

FIGURE 3 TAC/TAD plot. Points A and B represent the thrice- and twice-weekly regimens, respectively, with performance parameters given in the frame. Movements of the point in the thrice-weekly regimen caused by changes in different patient- and treatment schedule-related parameters are indicated by arrows. It is obvious that TAD is significantly influenced only by a change in frequency of dialysis sessions within a week. pcr = protein catabolic rate normalized per kilogram of body weight and/or residual renal clearance (KR).

value. This is illustrated in the figure by the shift from point A (thrice-weekly HD) to point B (twice-weekly HD).

Target values in the TAC/TAD plot

The TAC/TAD approach, although applicable in principle to plasma level fluctuation of any substance, can most easily be used as an extension of the conventional UKM. However, most deterministic mathematical theories applied in medicine for the assessment of the treatment outcome have target or limit values of deterministically given assessment parameters. These have to be found by statistical correlation of the deterministic parameter with some "fuzzy" clinical parameters. Such statistical study in fact forms a bridge between the simplified deterministic description of the patient's organism by means of a suitable model and the far more complicated real biological system. For UKM, an example of such a value is Kt/V = 1 found in the well-known National Cooperative Dialysis Study (NCDS) (8).

The TAC/TAD concept was developed as a theoretical tool (7) and, in fact, has never been tested in any multicenter large-scale study of the NCDS type. Nevertheless, desirable development of the treatment schedule representation in the TAC/TAD plot can be derived from Figure 4. However, for target values of TAD in particular, clinical or biochemical parameters will have to be identified that show a clear interrelation with the treatment schedule. Suitable candidates may, for instance, be a toxic substance, generation of which will be augmented by abrupt osmotic changes, which are characteristic of low-frequency dialysis schedules.

Applications of the TAC/TAD concept

Based on well-elaborated simulation possibilities of conventional UKM, the TAC/TAD concept can be used both for retrospective and prospective evaluation of different HD and PD schedules. With regard to very favorable reports on daily HD, this modality seems to be very tempting for the future, especially when HD can be performed at the patient's home. The results obtainable with increasing frequency of dialysis

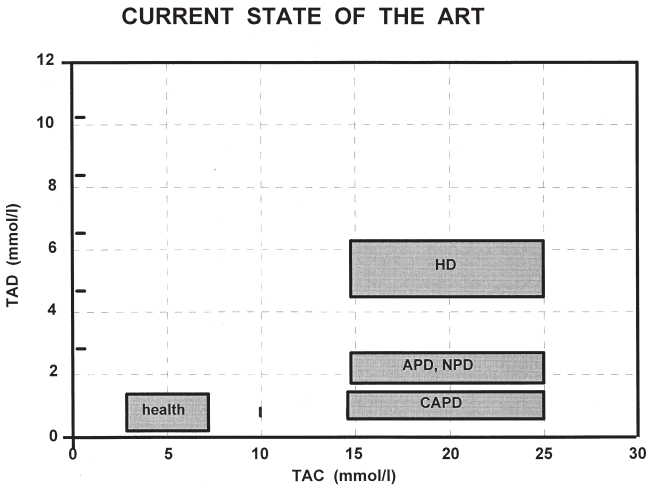

FIGURE 4 State-of-the-art in different renal replacement therapy modalities in the TAC/TAD plot. The areas illustrated correspond to TAC/TAD values in patients on hemodialysis (HD), automated or nightly peritoneal dialysis (APD, NPD), conventional CAPD, and in a healthy population.

sessions are well documented in Figure 5. It is obvious from the figure that values of both TAC and TAD, which would fall in the "health region" as shown previously in Figure 4, can only be obtained with the use of highly efficient dialyzers in frequent schedules. This conclusion may be somewhat surprising for those who thought of a trade-off between frequency of dialyses and dialyzer clearance.

Limitations of the TAC/TAD concept

Although the two-dimensional approach of the TAC/TAD concept offers a more complete picture of the dialysis treatment outcome than the conventional one-dimensional UKM, it does not offer a complete algorithm for setting up a dialysis strategy. TAD is not very sensitive in distinguishing between intermittent regimens with equal and unequal partition of dialysis sessions within a week, and it cannot distinguish between the short, highly efficient dialyses and longer and milder dialyses. While the former issue has already been subject to theoretical analysis (9), theoretical tools for the latter are still to be developed. Intercompartmental concentration gradients for small molecular weight substances such as urea induced by too rapid dialysis may be a suitable parameter, namely, for acute dialysis. For chronic dialysis treatment, high ultrafiltration rates typical for ultrashort, highly efficient schedules are more likely to be a limiting factor. Entirely different parameter(s) may also be introduced to deal with the issue of intermittent treatment unphysiology, such as the recently suggested concept of the kinetic treatment period (10). In any case, regardless of the mathematical definition of such a parameter, suitable clinical correlates will have to be identified before the unphysiology concept is practically applied for optimization of any renal replacement therapy.

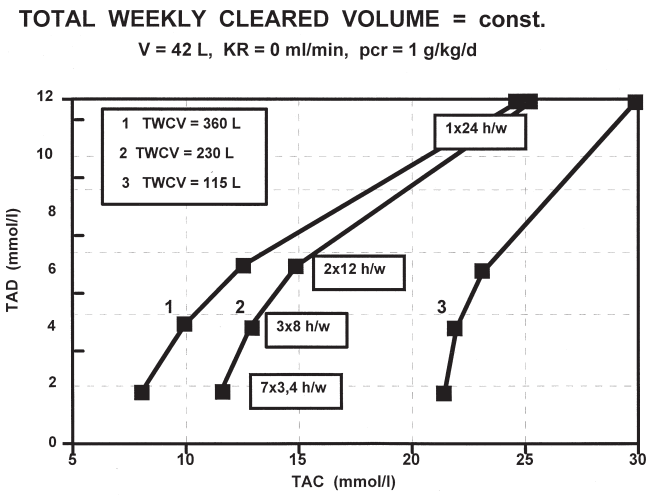

FIGURE 5 Limits of the intermittent treatment schedules seen in the TAC/TAD plot. Each curve has been calculated for a different value of the total weekly cleared volume. The differences were achieved by varying the clearance values (250 mL/min for curve 1, 160 mL/min for curve 2, and 80 mL/min for curve 3). The four points on each curve from the top to the bottom represent regimens with one, two, three, and seven dialysis sessions per week.

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