Quantification of dialysis unphysiology

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Introduction

It was in the middle of the last century that Claude Bernard created his concept of stability of the ‘milieu interieur’, for which later the term ‘homeostasis’ began to be used. Since then, this concept has become a cornerstone of physiology, to be precise of physiology of any intact organism. Dr George Schreiner, one of the pioneers of dialysis, obviously recognized the validity of this concept in the field of artificial organs in the early days of dialysis, postulating that: ‘Homeostasis applies not only to organisms but also to the artificial organs and to the peculiar relationship which must develop when a person and a thing are coupled for survival.’ (1959). However, the rather low efficiency of dialysis devices of that time was just enough to ameliorate the uraemic state of a patient without further worsening of the already disturbed homeostasis. Logically, the efforts of early dialysis researchers were thus directed towards increasing the dialysis efficiency. In the mid-1970s, when dialysis became so efficient that it could cause serious disruption of the already disturbed homeostasis of patients with renal failure, it was Kjellstrand [1] who for the first time drew attention to the issue of possible negative effects of the unphysiology of intermittent dialysis treatment. However, his concerns were partly solved a few years later by the successful reintroduction of bicarbonate dialysis, and economic pressures probably contributed further to another period of neglect of the issue. The physiology of intermittent haemodialysis (HD) treatment became topical again when confronted with apparently very good results of continuous ambulatory peritoneal dialysis (CAPD), the efficiency of which was far less than that of HD. Also some long-term complications in HD patients have been attributed speculatively to abrupt changes in the ‘milieu interieur’. However, development of any mathematical theory or of any other system of quantification of dialysis unphysiology has not been attempted despite wide application of mathematics in this field of medicine. The works published in the late 1980s and early 1990s on inter-compartmental concentration disequilibrium and the immediate post-dialysis rebound phenomenon cannot be counted, as those were oriented towards more precise definition of the delivered treatment dose rather than the physiology of the treatment strategy.

Definition of haemodialysis strategy and its physiological implications

What is behind the expression ‘setting-up of dialysis strategy’? If we ignore for the moment the issue of molecular weight removal profile which is determined by membrane properties and by the magnitude of the convective component, to set up a treatment strategy means to select three parameters: (i) the clearance ($K_d$); (ii) the length of the dialysis session or treatment time ($T_d$); and (iii) the frequency of dialysis, i.e. the number and distribution of dialysis sessions in a week ($n$).

Values of these three parameters should be selected in such a way that the treatment outcome would be optimal or at least acceptable. In other words, some variables or criteria were needed whose values could be easily measured and easily or directly influenced by the above three selectable treatment parameters.

From the purely mathematical point of view, the number of independent criteria or criterion functions must equal the number of parameters to be optimized. The dialysis index (DI), as introduced by Babb et al. [2], is an example of such a criterion. However, because DI is expressed by one equation only, two parameters of the above-mentioned three had to be chosen arbitrarily, and only the third one could then be calculated in such a way as to obtain $DI > 1$.

In conventional urea kinetic modelling (UKM) [3], the two following target treatment outcomes, or, in mathematical terminology, optimization criteria, were introduced. The very first version worked with plasma urea TAC (time-averaged concentration) and protein catabolic rate (PCR). This was later simplified when the mid-week pre-dialysis plasma urea level was used, again with PCR. Finally, the currently most widely used concept of $K_t/V$ and PCR evolved. However, because PCR was regarded as an independent variable...
not directly controllable by the treatment strategy parameter selection, UKM also left us with only one criterion, be it the target value of TAC, $C_{\text{pre}}$ or $Kt/V$, from which only one parameter out of the three, $K_d$, $T_d$ and $n$, could be established after an arbitrary choice of the other two.

For instance, it is possible to reach the same TAC in a patient both on a twice-weekly regime and on a thrice-weekly schedule (Figure 1a). By keeping the same clearance but prolonging the dialysis time, we can even obtain the same maximal pre-dialysis urea concentration in both schedules (Figure 1b). However, we intuitively feel that the thrice-weekly schedule will be more physiological and the patient on that regime will receive higher quality treatment as compared with the twice-weekly regime. The question now is how this intuitive perception of treatment schedule physiology could be quantified.

**Quantification of dialysis schedule unphysiology**

In engineering sciences, the quality of a control process (and dialysis can be indeed be viewed as a control process targeted towards normalization of the ‘milieu intérieur’) is often described by a time integral of the deviation of a controlled variable from its target value. Similarly to this and in analogy with the definition of TAC, we have complemented conventional UKM by a new parameter—TAD (time-average deviation) (Figure 2). Defined in this way, TAD represents mean deviation of plasma urea concentration from the TAC [4].

Obviously, the less frequent and thus less physiological the treatment schedule, the higher will be the fluctuation that the plasma concentration will exhibit and the higher the resulting TAD. This parameter may thus be used to describe the unphysiology of a given dialysis schedule.

Treatment outcome of a specific treatment schedule can now be represented by a point on the TAC/TAD plot, and a sensitivity analysis of parameters involved in the plasma urea concentration profile can be performed (Figure 3). While $K_d$ and $T_d$ influence TAC only and have practically no impact on TAD, patient parameters, e.g. residual renal clearance (KR) and urea generation rate $G$ (or PCR), influence both TAC and TAD. From among the treatment parameters, TAD can be influenced effectively only by a change in dialysis frequency. See shift from point A to point B in Figure 3.

**Retrospective and prospective application of the TAC/TAD concept**

It is useful to inspect development in dialysis strategy retrospectively over the last three and half decades with regard to the TAC/TAD plot (Figure 4; calculations were done for the patient’s parameters indicated in the figure by means of a two-pool model of urea kinetics): In 1960, Hegstrom [5] dialysed patients for 24 h once weekly on a Kiil dialyser which had a urea clearance of some 80 ml/min (point A). Both TAC and TAD were quite high. To improve the status of his patients, Hegstrom instituted a twice-weekly schedule, with each session lasting 12 h (point B) [6]. On home HD patients, he was later even able to change to a thrice-weekly schedule with the same technology (point C). Siddiqui and Kerr [7] recommended dialysis with the Kiil dialyser for 10 h thrice weekly, and with the more effective coil dialyser three times for 8 h per week (point D). Point E represents schedules considered standard today ($3 \times 4$ h with a clearance of some 150–170 ml/min; once considered short!) and point F shows ultrashort highly efficient treatments ($3 \times 2.5$ h with a clearance of 250 ml/min). The conclusion is by no means very encouraging; from the point of view of urea kinetics, there has been no progress made over the last 5–10 years. Rather, the contrary is true, at least as assessed by TAD values.

Mathematical simulation can also be used to assess the limits of renal replacement therapy applied intermittently (Figure 5). Each of the curves plotted in this...
Fig. 2. Definition of time-averaged concentration (TAC) and time-averaged deviation (TAD).

Fig. 3. Sensitivity analysis in the TAC/TAD plot.

Figure has been calculated for a different value of the total weekly cleared volume, again by means of a two-pool model. The differences in curves were achieved by using a different, but for a given curve constant, clearance value. The lowest point of each curve represents daily HD. As can be seen, more frequent dialyses influence the TAC more, with higher weekly cleared volumes. This leads to the somewhat surprising conclusion that the potential of highly efficient dialysers can be utilized fully only in frequent treatment schedules.

Fig. 4. Retrospective assessment of dialysis treatment evolution.
What should the target be?

Inspection of Figure 3 reveals which parameter of the dialysis strategy can be altered to move the patient’s point in the desired direction. Logically the question must arise: where should the point be, what is its target position?

While a not very encouraging yet true answer to this question is ‘we do not know’, it is certainly possible to seek some inspiration from Figure 6. It displays approximate areas of currently used treatment modalities, HD, CAPD and automated or night peritoneal dialysis (APD, NPD), and also the area typical for full health.

As for the acceptable TAC value, the results of the legendary NCDS study [8] indicate that TAC should be kept below 18 mmol urea/l [which corresponds to 50 mg/dl of blood urea nitrogen (BUN)].

With regard to the acceptable TAD value, there are no statistical studies available where a correlation of this parameter with morbidity or dialysis-associated disorders could be found. Enough material for a retrospective evaluation on TAD could be provided only by those centres that have used non-conventional dialysis schedules (every-other-day or daily dialysis) in sufficient numbers of patients and for sufficiently long periods of time. In doing such a study, one should focus on those adverse effects described in dialysis patients which might be related to dialysis unphysiology, such as unphysiological cyclic stress of cell membranes suspected to contribute to accelerated ageing of these patients, the hypothesis on stimulation of β2-microglobulin generation by abrupt changes in osmolality of body fluids [9] and lowered PCR during long interdialytic periods [10]. A more detailed view of different treatment modes and schedules as compared with Figures 5 and 6 can be obtained from Table 1.

The values in Table 1 were generated for an average patient with total body water of 42 l, negligible residual renal function and a PCR of 1 g/kg/day dialysed with a urea clearance of 160 ml/min for the same total weekly time (and thus equal weekly cleared volume). Seeing the rather small differences in TAD in equally and non-equally distributed dialyses in a week, one can question the appropriateness of using the mean values. Peak values could certainly be used instead. However, mean values are the most effective protection against the excessive influence of a single laboratory error on the overall assessment.

Limitations of the TAC/TAD concept

While the TAC/TAD concept can be used to quantify the unphysiology of a treatment schedule, it is not a complete algorithm for optimization of dialysis strategy. Although a target value of TAD determines the necessary frequency of treatment sessions in a week, the target value of TAC determines the necessary
treatment dose, i.e. the product of dialysis time and clearance, similarly to conventional UKM.

To distinguish between short, highly efficient treatment and treatment performed with lower clearance but for longer time, i.e. to quantify the unphysiology of a single session, some other tool would have to be developed. It could be based on the computed inter-compartmental concentration gradient or a change in cerebrospinal fluid pressure. While its value for chronic HD would most probably remain rather academic, it might prove to be quite useful for setting-up the limits in acute HD efficiency and/or duration.

References