Rationale for Daily Dialysis

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The kidneys maintain the body's homeostasis by removing water and waste products continuously and efficiently. The ideal dialytic treatment should emulate the functions of the kidney. Of the dialysis treatments currently available for chronic renal failure, the only continuous ones are continuous ambulatory and continuous cyclic peritoneal dialysis; however, the efficiency of peritoneal dialysis is limited by the nature of the peritoneal membrane. Extracorporeal dialysis is markedly more efficient than peritoneal dialysis, but is performed intermittently (usually 3 times/week) with large fluctuations of body fluid volumes and concentrations of various solutes and electrolytes. These fluctuations cause intercompartmental disequilibrium during dialysis, induce intradialytic and interdialytic symptoms, and create difficulties in controlling blood pressure. Daily dialysis is both frequent and efficient and therefore seems to be superior to any other form of renal replacement therapy.

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Key words

Peritoneal dialysis, dialysis disequilibrium, blood pressure control

Introduction

The kidney, in addition to its hormonal and metabolic functions, also maintains the body's homeostasis by removing water and solutes continuously and efficiently according to its variable needs. The ideal dialytic treatment should compensate for this clearance function lost in patients with end-stage renal disease (ESRD) by emulating the kidney quantitatively and qualitatively. The treatments currently available still have not fully reached this goal. In order to be truly adequate, treatment for ESRD should fulfill many different requirements. The treatment should:

1. remove all types of uremic toxins and the electrolytes abnormally accumulated, and do this in a sufficient quantity to prevent their toxic effects.
2. remove the retained water in a sufficient quantity to prevent a clinically relevant volume expansion and its acute and chronic consequences (hypertension, cardiac overload and hypertrophy, cardiac failure).
3. correct the alterations of the acid-base equilibrium.
4. accomplish all the above-mentioned functions in a manner as naturally as possible, which is continuously, and thus avoid the oscillations in levels of toxins, electrolytes, water, and bicarbonates in the blood.
5. fulfill these goals with no or minimal interference in the work and social lives of the patients.

None of the currently available treatments fulfill these requirements completely, including the most recent and sophisticated modalities such as hemodiafiltration, acetate-free biofiltration, and paired filtration dialysis.

In fact, removal of uremic toxins remains largely unsatisfactory both for the quantity and for the range; the complete removal of water can be achieved in only a minority of cases and even then with some difficulty. The majority of ESRD patients still have hyperphosphatemia and remain acidotic most of the time, and, above all, the predialytic and postdialytic oscillations in levels remain unphysiological. Consequently, the patients remain in poor clinical condition, the rehabilitation is modest, the quality of life is usually poor, and morbidity and mortality remain high.

Causes of the failure of the current dialytic strategies

Clearly, only a treatment that is continuous can best approximate the clearance function of the kidney.

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Practically, of the dialytic treatments currently available for chronic renal failure the only continuous ones are continuous ambulatory peritoneal dialysis (CAPD) and continuous cyclic peritoneal dialysis (CCPD). However, even this treatment has considerable limitations, essentially in the membrane, which has limited efficiency and is not replaceable.

As for the extracorporeal dialytic treatments (awaiting the presently chimerical, bionic artificial kidney), the treatment times used are all intermittent and the frequency of sessions is relatively low, with lengthy intervals between. We are still searching for the best compromise between the conflicting needs of achieving the possible best clearance and minimizing interference with the patient's life. However, in this search the efforts have been focused exclusively towards a reduction in the session length, which, excluding any variation in the frequency, implies an increase in the speed of the removal to maintain the same total solutes per session. This approach soon proved to generate a lot of problems and negligible advantages, in spite of the apparently adequate Kt/V values. In fact, on the one hand, the effort to increase the removal by increasing clearance and Kt/V is rapidly made ineffectual by the *self-limiting effect arising from the multicompartmental distribution of solutes*. Due to this, in fact, the increased speed of solute removal from the small intravascular compartment cannot be timely compensated for by the refilling from the other compartments, which becomes slower even for the most diffusible toxins, like urea. This discrepancy induces a more rapid decrease of the blood concentration and, consequently, of the blood-dialysate gradient, which is the driving force for the diffusion of the solutes, as clearly shown in Figures 1 and 2, which display very good correlation between urea extraction and predialytic blood levels.

Consequently, a rapid decrease in the mass transfer coefficient will occur, which becomes more evident the longer the session, so that the final result in terms of blood levels and, above all, of solute removal, will be much more limited than one could expect and largely disproportionate to the entity of the increase of clearances and Kt/V.

Also, according to the discussion made recently on the same subject by Depner (1,2), this behavior could be efficaciously represented graphically, as in Figures 3 to 5.

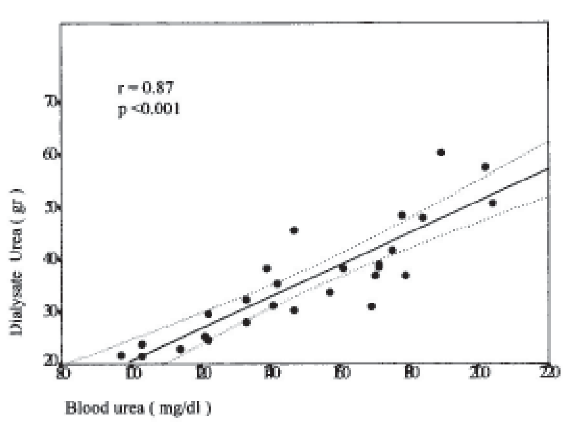

FIGURE 1 Correlation between predialytic blood urea values and urea extraction (4-hour dialysate collection).

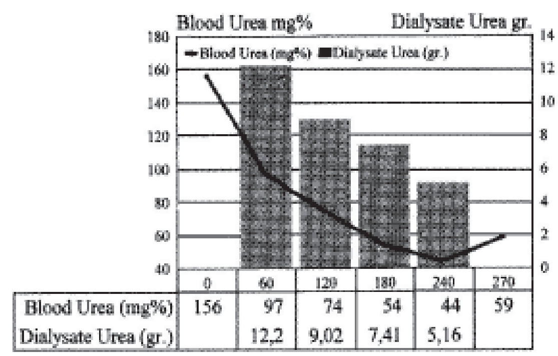

FIGURE 2 Urea extraction and blood levels in 4-hour standard hemodialysis (S-HD).

The progressive increase in the clearance generates a progressively more rapid decrease in plasma levels of solutes during the first part of the session (Figure 3) and vice versa as a direct consequence of the gradient's dissipation, a progressively less rapid decrease during the second part, the curve being progressively switched to the left and more vertical during the first 2 hours and leveling off thereafter. The maximum difference between the curves tends to be progressively anticipated as the efficiency increases (Figure 3). A similar, rapid decrease occurs with the fractional removal during the session, but with curves

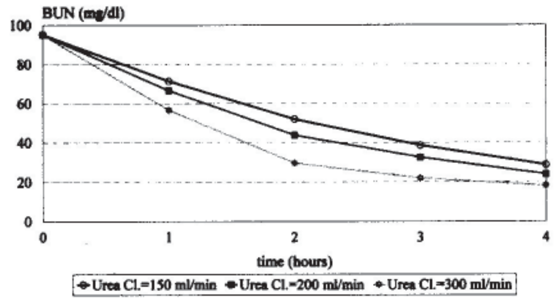

FIGURE 3 Decrease in blood urea nitrogen (BUN) levels throughout the session at different clearances.

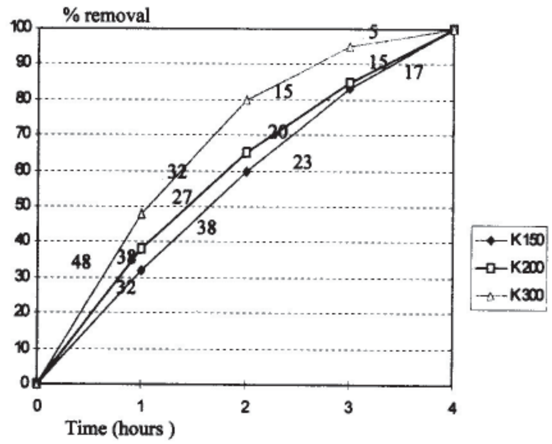

FIGURE 4 Hourly removal (percent) of urea throughout a 4-hour dialytic session at different clearances (K).

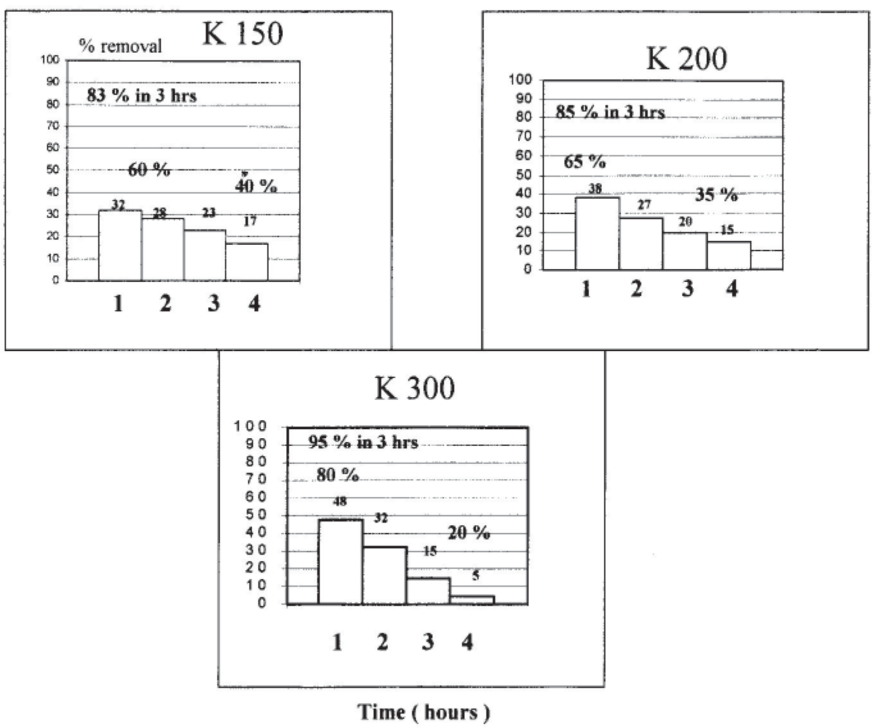

FIGURE 5 Different graphical representations of the percent urea removal at different clearances (K).

(Figure 4) specular to the curves of the blood levels in Figure 3; most of the removal occurs during the first half of the session and in a proportion progressively higher with the increase in clearance. In many cases, as in the hypothetical case illustrated, very high clearances can constitute, within the first 2 hours, up to 80% of the total clearance of an entire 4-hour session. This is even more evident in Figure 5, which represents the phenomenon in a different way; it is clear that at very high clearances, keeping the length of the session stable at 4 hours, the contribution during the last 2 hours to the global solute removal becomes minimal, while it is maximal during the first 2 hours. Under these conditions of very high efficiency, which is at the moment difficult to achieve in clinical practice, the absolute removal obtainable within the first 2 hours could be equal or even superior to that obtained with a standard efficiency 4 hours hemodialysis (HD) (see also Figure 6). However, this would not be the case if the clearance increase were not so extreme; removal within the first 2 hours will remain lower than that achieved with standard HD (Figure 6), and to shorten the session length to this point could be dangerous and could worsen the uremic syndrome, as it seems to have sometimes happened with the ultrashort high-efficiency HD.

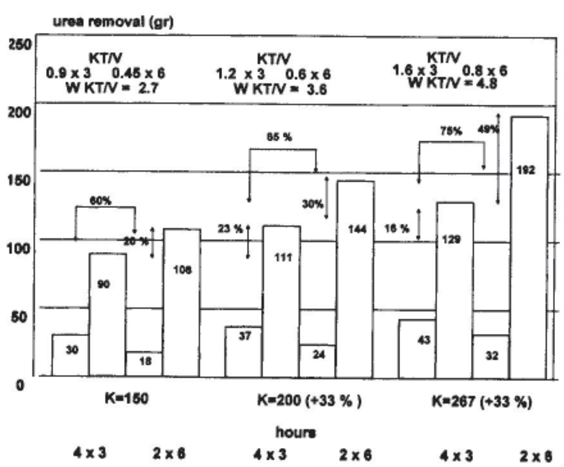

FIGURE 6 Comparison of the absolute and percent urea removal, per single session and per week, with standard hemodialysis [4 × 3 (4 hours, 3 times/week)] and with daily hemodialysis [2 × 6 (2 hours, 6 times/week)] at different clearances (K).

On the other hand, apart from this very important self-limiting effect on the effective removal of solutes, the high efficiency, especially when combined with a long period of time between sessions, generates sharp predialytic and postdialytic variations in the blood concentrations, and accentuation of their postdialytic rebound and of the intercompartmental disequilibrium, the underestimation of which could have been responsible for the apparently good but fallacious end dialytic values obtained with the ultrashort high-efficiency HD. This unphysiological condition, which is responsible for accentuated cellular and vascular stress, has been mathematically defined by Lopot and Valek (3), who introduced the concept of the time-averaged deviation (TAD) of urea blood concentrations with respect to time-averaged concentration (TAC) as an expression and measure of the treatment's physiology.

Considering that in the patient with a normal kidney the TAD remains steadily around zero, a substitutive treatment for ESRD will be physiological, because it will be able to maintain this index as low as possible in the patients. Such a goal can be reached only through a treatment that is continuous (in the current clinical practice, only by CAPD or CCPD), while the unphysiology, as expressed by high TAD, increases with the length between sessions and with the increase in the efficiency of the sessions. Thus TAD and unphysiology have remained high during the last 20 years of treatment with all types of extracorporeal dialysis, due to the unchanged frequency of the sessions and have even further increased during the last years with the introduction of highly efficient techniques.

From all these considerations it is clear how the dialytic strategy pursued until now (i.e., to increase the clearances while maintaining or even reducing the session length without increasing its frequency) was erroneous. While it has failed to improve the quantity of clearance, it has increased the dialysis-related problems, requiring a number of technical innovations (high Na concentrations, modulation of Na and ultrafiltration, continuous monitoring of body weight, heart rate, blood pressure, blood volume, mixed diffusive-convective techniques), which have merely served to counteract these side effects, considerably increasing the costs.

Thus there is urgent need to explore new strategies that enable a higher and more physiological clearance, possibly with simpler and less expensive systems. As long as a continuous extracorporeal dialytic treatment is not feasible, due to the multicompartmental structure of the organism, the only way to approach the ideal treatment both quantitatively and qualitatively is therefore to increase the only parameters that have remained paradoxically unchanged for such a long time: the schedule and, above all, its frequency. One way to realize this practically is to perform more frequent, low efficient but long-lasting sessions, as proposed by Uldall (4). This approach could have some advantages, like a greater removal of middle molecules and phosphates and extremely reduced TAD and rebound. However, even when performed during the only reasonable part of the patient's day, that is, during the night, this approach does have disadvantages (possible disconnection of the lines with blood loss and air embolism, interference with sleep, clotting or infection of the central venous catheter). This is why we extensively explored a more feasible alternative, ultrashort daily HD (5–7), which, performed during the daytime or evening for such a short time (2 hours), does not interfere with the patient's work and social life, while eliminating the risks and the problems related with a long nocturnal unattended dialysis.

Rationale of ultrashort daily HD

From a theoretical point of view (Figure 6), 2 hours of standard efficiency dialysis (clearances of 150 – 200 mL/min), even if performed only 6 times/week, will significantly increase the weekly removal of urea compared to the corresponding standard HD (4 hours, 3 times/week), by employing exactly the same total time per week (12 hours resulting from either 2 × 6 or 4 × 3). Figure 7 shows the weekly urea extraction in 9 patients during 2 consecutive weeks of study, the first while on standard HD 3 times/week and the second on short daily HD; all other dialytic parameters unchanged. Most of the urea removed (60% – 65%) during an entire session (4 hours) takes place during the first half; therefore, limiting the session length to the first 2 hours will reduce the removal per session by 40% and 35%, respectively (from 30 to 18 g and respectively from 37 to 24 g for the two different clearances in the hypothetical examples depicted in Figure 6, derived from our direct clinical experience), but it will produce a significant increase on a weekly basis (respectively of 20% and 30%, from 90 to 108 g/week and from 111 to 144 g/week). The gain in terms of absolute, global weekly removal with short daily HD with respect to standard HD increases progressively (up to 49% in the example) with the increase in the clearance, which increases the percentage removal up to 75% during the first 2 hours. However, from the same figure, Figure 6, it appears how, on the contrary, the proportional removal becomes relatively less efficient by excessively increasing the clearance while maintaining a standard schedule. With this schedule, in fact, the discrepancy between the increase in clearance and the proportional weekly removal, which is already evident after increasing the clearance from 150 to 200 mL/min (23% increase of the removal vs a 33% increase of the clearance), becomes even clearer after an equivalent increase (33%) of the clearance from 200 to 267 mL/minute (increase of removal of only 16%). It is logical to conclude that it is highly advantageous to use high clearances coupled with an increase in the frequency, despite the reduction in the length of the session.

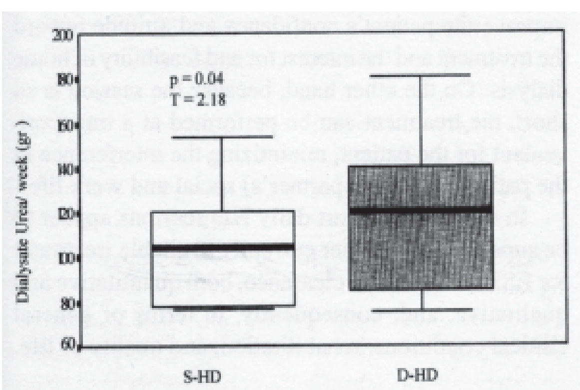

FIGURE 7 Weekly urea extraction in 9 patients during 2 consecutive weeks on standard hemodialysis (S-HD) and daily hemodialysis (D-HD). T = Student's *t*-test.

In clinical practice, however, this particularly favorable situation will be partially blunted by the fact that during the first 2 to 3 weeks the predialytic blood levels will progressively decrease until a new steady state is reached. Thus the urea extraction per session also decreases, so that the real advantage in terms of weekly urea removal is reduced and, at least

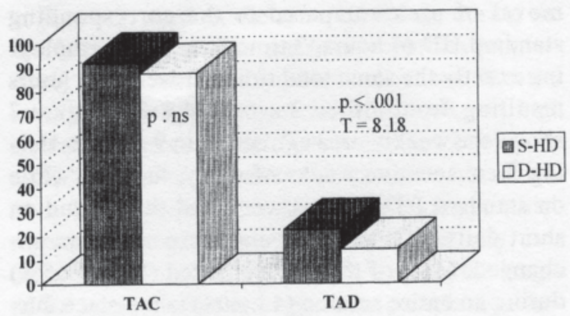

FIGURE 8 TAC (time-averaged concentration) and TAD (time-averaged deviation) in daily (D-HD) versus standard hemodialysis (S-HD). T = Student's *t*-test.

with the lower clearances, almost completely nullified. However, a new equilibrium is reached, which is more advantageous for the patient, since the peak concentrations of solutes (urea, creatinine, K, H^+) throughout the week are reduced, as are also the TAC and TAD (Figure 8).

Moreover, we have to take into account three other decisive advantages of the daily schedule: the much improved control of acid-base equilibrium and the almost perfect control of fluid balance, both intradialytic and interdialytic. In fact, the blood values of pH and bicarbonate remain steady within the normal range, with acidosis practically disappearing.

Intradialytic water removal is extraordinarily easily performed, even up to 1 L/hour or more, without evidence of cardiovascular instability and easily achieving the true dry weight, which will greatly contribute to preventing the chronic fluid overload typical of the patients treated with the standard thrice-weekly schedule and the main factor responsible for the high rate of hypertension in this population.

Discussion and conclusion

More frequent extracorporeal dialysis (6 to 7 times/week), with a shorter duration of the sessions but with the same cumulative time/week, appears, at present, to be the most convenient and feasible approach to the ideal treatment for ESRD.

In fact, it allows a higher removal of urea by overcoming the limiting effect of its multicompartmental distribution, especially by using very high clearances. This seems to suggest, at least theoretically, a particularly profitable way to exploit to the utmost the potential of high clearances in combination with the daily schedule and short sessions. It is questionable and still has to be proven whether it will add further significant clinical advantages, and will be worth facing the potential disadvantages (a certain increase of disequilibrium, rebound, and TAD); disadvantages which, however, would tend to be self-limited and would decrease with time, together with the progressive reduction in the predialytic urea levels.

However, apart from the increase in removal, this approach has significant advantages: reduction in peak concentrations, TAC, and TAD, reduction in predialytic and postdialytic oscillations in solute concentrations, and in postdialytic rebound. All these result in a lower degree of toxicity and in a higher degree of physiology. Then we have perfect control of acid-base equilibrium, which, normally being steady in the blood would also be normal in the cells. This may, in turn, have a tremendous, positive impact on various metabolic aspects, by improving the normalization of a wide variety of enzymatic steps, hampered by the unphysiological uremic environment and pH. Furthermore, good fluid balance control, made possible by many factors (reduction of thirst following the reduction in the solute concentration, reduction of interdialytic intervals, shortness of the sessions, which do not allow enough time for the manifestation of a significant contraction of blood volume and of the possible vasodilating effect of cytokines), prevents intradialytic hypotension and interdialytic hypertension, thus reducing cardiovascular morbidity and mortality. The improvement in general clinical conditions will improve the patient's confidence and attitude toward the treatment and the interest for and feasibility of home dialysis. On the other hand, because the session is so short, the treatment can be performed at a time convenient for the patient, minimizing the interference in the patient's (and the partner's) social and work life.

In conclusion, short daily HD sessions appear to be superior to any other currently available treatment for ESRD in terms of clearance, both quantitative and qualitative, and, consequently, in terms of general clinical conditions, rehabilitation, and quality of life.

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