EDITORIAL

The Middle Molecule Hypothesis Revisited. Should Short, Three Times Weekly Hemodialysis Be Abandoned?

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When the middle molecule (MM) hypothesis was formulated in 1975, no MM had yet been identified as a uremic toxin. Meanwhile, the birth and implementation of the Kt/V_{urea} concept gained wide acceptance and has remained the world standard for assessing dialysis adequacy. However, over the past 20 years, accumulating evidence has made it clear that MM's are important uremic toxins, and that the dose of dialysis based on removal of small molecular substances does not protect against excessive hemodialysis mortality, morbidity, or the presence of uremic signs and symptoms. These poor results are, in one way or another, linked to the accumulation of MM's and other substances behaving like MM's, such as phosphate.

Dialysis schedules yielding the best clinical results, such as longer dialysis and more frequent dialysis, favor increased removal of middle molecular substances. The observation that short daily dialysis is giving results similar to long nocturnal quotidian dialysis supports early observations that the volume from which middle molecular substances are extracted mainly by hemodialysis is small (about as large as the extracellular volume), and that transfer of MM's from cells to extracellular fluid is very slow. This behavior of MM's is markedly different from that of small molecular substances, which are more rapidly transferred from intracellular to extracellular compartments and are more readily extracted from total body water during hemodialysis.

In order to achieve even minimum adequate dialysis, it is now scientifically validated that toxic MM's must be removed in larger amounts than currently attained. This can only be accomplished by long dialysis sessions with a 3-times per week schedule or more frequent dialyses. Five hours 3 times per week represents the absolute minimum treatment. Dialysis 6 to 7 times per week is the ideal schedule for patients who are willing to commit the time and effort in exchange for maximum well-being and long survival.

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Introduction

The middle molecule (MM) hypothesis, based on a number of interesting observations in chronic dialysis patients in the 1960s, was proposed by Babb in the 1970s [1]. This paper provides support for the idea that some MM's are important uremic toxins and, therefore, reliance on the current guide to an adequate dose of dialysis, Kt/V_{urea}, without considering MM removal may lead to underdialysis. The standard hemodialysis (HD) schedule (3×/wk, 3 – 4 hours) as currently practiced cannot provide truly adequate dialysis in anuric patients, even though it meets the recommended Kt/V_{urea}.

The size spectrum of MM's varies according to author, from 500 to 5000 [1], 300 to 12,000 [2], and 10,000 to 50,000 daltons [3], but a broader definition must prevail to give the concept its full significance. This includes the smaller solutes behaving in dialysis as MM's either because of slow intercompartmental transfer (phosphate, peptides) or protein binding (methylguanidine, hippuric acid, homocysteine). For these solutes behaving like MM's, removal is affected more by session time but "less by larger pore size" [4], except possibly when using a protein-permeable membrane [5].

Historical perspective

A retrospective analysis of the early Seattle dialysis experience reveals that, by chance, we had the good fortune to start with long slow HD [6], a dialysis technique that, in retrospect, was favorable for the removal of MM's. As a result,

our early success with patient quality of life and survival [7] might have been due in part to the fact that we unknowingly were using a dialysis technique that accomplished a much larger removal of toxic MM's than other earlier investigators, all of whom were using the Kolff twin coil [8]. Using the Seattle continuous flow HD system [6], weekly time on dialysis was roughly twice as long as was possible with the old twin-coil system. Back in the early 1960s during an American Society for Artificial Internal Organs meeting, Dr. Kolff challenged Dr. Scribner, who was claiming better success with long slow dialysis, to accept one of his HD patients for a trial of the Seattle dialysis method. The clinical response was amazing and included reversal of uremic neuropathy, return of appetite, and real weight gain. Since the weekly clearance of urea was roughly the same with 2 × 6 hours per week treatments on coil dialyzers versus 2 × 12 hours/week on Skeggs/Leonards dialyzers, both using DuPont 300 membrane (Globe Paper Co., Cleveland, OH, U.S.A.), this response may have been due to increased dialysis time with an accompanying increase in toxic MM removal.

After 1965 when the Skeggs/Leonards dialyzer was replaced with the Kiil dialyzer, MM clearance got an additional boost because the new membrane, Cuprophan (J.P. Bemberg, Wuppertal, Germany), that the Kiil employed was much thinner than the DuPont 300 membrane used in the Seattle continuous flow system and in the twin coil used by other centers. Therefore, by inadvertently using dialysis techniques that provided high MM clearances, survival of the first Seattle patients was indeed remarkable [7].

Middle molecules and uremic neuropathy

As detailed elsewhere, the earliest guide to an adequate dose of dialysis was that amount necessary to reverse uremic neuropathy [9]. This clinical observation then led to the hypothesis that toxic MM's were associated with the development of uremic neuropathy. A series of experiments and careful review of previous data on neuropathy verified this important cause-and-effect relationship [9].

A brief review of the case histories of the 3 original Seattle patients presents a wide spectrum with respect to the severity of uremic neuropathy [10]. In retrospect, this review reveals how toxic MM's and their removal by residual renal function can explain these marked differences in the severity of uremic neuropathy in these 3 patients.

Patient A, a 24-year-old male, was in uremic coma when started on chronic dialysis. He was anuric. Although his coma responded to dialysis, he developed severe permanent motor nerve damage. Patient B, a 36-year-old male, had considerable residual renal function at the start of dialysis, which gradually was lost in the first few months. Shortly thereafter, he developed uremic neuropathy, which was arrested by increasing the frequency of dialysis from 1×/week for 24 hours, to 2×/week for 12 hours. Patient C, a 20-year-old male, retained some residual renal function well into his second year of dialysis. He never developed any overt evidence of peripheral neuropathy. In retrospect, residual renal function, although insufficient to sustain life, provided sufficient removal of toxic MM's to prevent Patient C from developing uremic neuropathy. This contention is supported by a study showing that renal clearances of MM substances in renal failure patients are as high as or higher than creatinine clearances [11].

In addition, the observation was made that early patients on chronic peritoneal dialysis did not develop neuropathy, despite poor small-molecule clearance [12]. This observation suggested that the peritoneum was clearing some neurotoxins more efficiently than the small-pore membranes in the early hemodialyzers [12]. Based on this observation, Babb *et al.* [9] first proposed the idea that these toxins might be of larger molecular weights than previously believed, and thereby originated the term "middle molecules." Later, Babb and others speculated that MM's pass through the peritoneum better than through the early dialysis membranes, and that indeed proved to be the case [13]. Peritoneal dialysis morbidity and mortality still seems comparable to HD, at least for the first few years of treatment, in spite of its much lower Kt/V_{urea}.

The high-efficiency hollow-fiber dialysis experiment and Kt/V_{urea}

In the course of early studies of MM removal, a prototype high-efficiency hollow-fiber hemodialyzer was fashioned by hooking three regular Cordis–Dow hollow fiber dialyzers in series to create a 3-m^2 unit [9]. Cordis–Dow was so impressed that they soon marketed a 2.5-m^2 dialyzer. In retrospect, this introduction of the high efficiency dialyzer had disastrous unintended consequences in terms of patient survival and well-being, because it facilitated shortening of dialysis session time to as little as 2 hours, based on Kt/V_{urea} as the index of adequate [14] or even minimally acceptable [15] dialysis.

It was unfortunate that urea was chosen as the marker molecule for the Kt/V_{urea} concept [14] because urea diffuses so rapidly that it fails to mimic the more slowly diffusing uremic toxins, some of which are in the MM size range. Thus, over the decades, belief in the Kt/V_{urea} concept as a reliable measure of an adequate dose of dialysis has permitted shorter and shorter dialysis times as the rate of removal of urea increased with improved HD technology.

Rotellar *et al.* argued that the time of dialysis could be safely shortened from 12 hours/week to 6 hours/week by doubling the dialyzer surface area from 2.5 m^2 to 5 m^2 [16]. Of course, short dialysis sessions also had tremendous patient appeal. As a result, the Kt/V_{urea} concept was in part responsible for the high mortality from its inception and testing in the 1970s, especially in the U.S.A., where short dialysis was carried to extremes [14]. In the 1990s, the mortality rate improved somewhat in the U.S.A. because the so-called safe minimum dialysis dose was raised in response to high mortality [14].

The Tassin experience

The same slow dialysis approach pioneered in Seattle has been employed in Tassin for over three decades [17–19]. Three

8-hour sessions per week led to an unusually high delivered Kt/V_{urea} of about 2.0 per dialysis and a relatively high MM removal. Although the case mix in Tassin has dramatically worsened over the years (increased age, proportion of diabetics, and cardiovascular comorbidity), the standardized mortality ratio has remained low, at about 45% of that in the U.S.A. as measured by its registry [19]. These data from Tassin are based on a study of over 1000 patients during the past quarter century [19].

Using the Cox proportional model, factors that might explain this good patient survival were examined. Survival correlated with the dialysis index, which measures MM removal, but not with Kt/V_{urea} [20,21]. This comparison is consistent with a recent analysis performed on the United States Renal Data System Case-Mix Adequacy Study cohort [22], and with the early, yet unpublished results of the HEMO study [23] pointing out the absence of improved survival when the single-pool Kt/V_{urea} is increased from 1.2 to 1.6 without changing frequency or duration of dialysis.

Over the past several years, the effect of switching 49 HD patients from 8 hours to 5 hours 3×/week has been studied [21]. With a Kt/V_{urea} almost unchanged (from 1.89 to 1.79, $p < 0.05$), shortening the dialysis session time was associated with impaired nutrition and blood pressure control [21]. Conversely, changing the dialysis schedule from 5 hours to 8 hours 3×/week led to improved nutrition and blood pressure control [21]. An important additional advantage of long dialysis sessions with gentle ultrafiltration is the possibility of successfully controlling hypertension while minimizing intradialytic hypotension [24].

Some MM's are uremic toxins

A typical uremic symptom is anorexia, which starts well before the patient reaches end-stage renal failure. A uremic patient with suppressed food intake may regain appetite soon after starting regular dialysis, presumably because of the removal of one or more toxic factors that suppress appetite. It has been clearly demonstrated that toxic MM fractions, isolated from uremic plasma ultrafiltrate and from normal human urine, injected intraperitoneally into conscious, free-moving rats, suppress consumption of orally infused carbohydrate or protein solutions in a dose-dependent manner [25]. The suppressive effect was found in fractions with a molecular weight range of 1 to 10 kD; fractions with lower molecular weight isolated from uremic plasma and normal urine had no effect on ingestive behavior, and all fractions isolated from normal human plasma were inactive as well. These results indicate that toxic MM's, which are normally excreted by the kidneys, accumulate in patients with uremia and cause or contribute to their loss of appetite. This is consistent with the observation that underdialyzed patients are malnourished, and that an adequate dose of dialysis improves both appetite and malnutrition. Severe uremic malnutrition is widespread among dialysis patients in the U.S.A., as indicated by the frequent use of intradialytic intravenous parenteral nutrition. A far better solution to uremic malnutrition is to provide an adequate dose of dialysis [26].

The hemofiltration experience

A prime example of how misleading the Kt/V_{urea} concept can be comes from the early results with pre-dilution hemofiltration using exchange volumes as low as 20 L 3×/wk [27]. Using this technique, survival and patient well-being were at least as good as with standard HD, undoubtedly as a result of a more efficient removal of MM's by convective transport. It is important to note that, in this study of hemofiltration, Kt/V_{urea} was in the very low range of 0.5 to 0.6 [27].

A recent comparison of convective and diffusive therapy again confirmed the benefits of convective therapy [28]. Mortality was 10% lower for patients treated with convective therapy, but the difference did not reach statistical significance ($p = 0.19$), while the 42% lower morbidity in terms of carpal tunnel syndrome surgery was significant.

Relevance of the emerging daily dialysis experience

Buoncristiani *et al.* [29] were among the first to describe the benefits of long-term daily HD. Not surprisingly, the introduction of long quotidian overnight dialysis by the Toronto group [30] has had an enormous impact on patient well-being. Patients that have gone from 3×/week dialysis with a high dialysis dose, as measured by Kt/V_{urea}, to quotidian overnight dialysis, have reported a remarkable improvement in well-being, a fact recently confirmed by Lockridge *et al.* [31].

What is rather surprising is that the patients of Buoncristiani and those patients that have recently changed to a 2-hour daily dialysis regimen also have benefited enormously [29,32]. Decreased swings in pre- and post-dialysis fluid volumes, concentrations of hydrogen ion, potassium, and other substances with daily dialysis, regardless of the length of sessions, may contribute to its beneficial effects on blood pressure, hematocrit, nutrition, and the general well-being of patients on daily dialysis.

According to Lindsay *et al.*, preliminary comparisons of long nocturnal and short daytime regimens show no clinical advantage of one or the other [33]. Obviously, this conclusion will need further clinical verification. A recent two-compartment mathematical model analysis comparing effective MM removal between short and long daily dialysis [34] clearly predicts the advantage of the long slow over the short fast daily schedule; however, there are no direct comparisons of various MM clearances between these two modalities. By direct measurement, Pierratos found a fourfold higher β_2-microglobulin clearance in nocturnal HD than in conventional HD [35]; Buoncristiani *et al.* reported markedly increased clearances of advanced glycated products in short daily dialysis [36]. If future comparisons between the two regimens show that the 2-hour/day schedule is almost as good in terms of MM clearance as the quotidian overnight approach, the explanation might be as follows.

As first suggested by Gotch *et al.* [37], a major problem with the dialytic removal of MM's may be the slow diffusion across the cell wall into the extracellular space. In other words, the intercompartmental clearances may be markedly lower than currently assumed. Back in 1979, the Stockholm group [38] showed that the decrease in MM concentration during dialysis was about as large as that of urea and creatinine, despite the lower dialyzer MM clearances. Whereas the initial rebound of urea and creatinine is rapid, MM concentrations increase slowly over the next 8 hours. The calculated distribution volumes from which the MM's were extracted were only about 30% of the body weight (about the volume of the extracellular fluid), that is, much lower than the distribution volume for urea and creatinine, which is about 60% of body weight. These results suggest there may be a diffusion barrier between cells and extracellular fluid that restricts the overall removal rate of MM's, and that, during a single dialysis, the reservoir from which MM's are being removed is the extracellular volume. If the dialyzer has a high MM clearance, it takes only a couple of hours to clear the extracellular space. If this theory is true, then the difference in net MM removal between a 2-hour/day schedule and an 8-hour/day schedule may be much less than predicted based on dialysis time alone.

Several years ago, Man *et al.* [39] showed this type of molecular movement for phosphate. They compared phosphate removal with 5-hour HD versus hemofiltration in 10 stable patients. Whatever the pre-treatment phosphate level or treatment modality, the initial high phosphate mass removal rate reached a steady-state level after 2 hours of treatment [39]. The mean intracellular phosphate efflux rate did not exceed 362 μmol/kg/hr. A more recent mass balance analysis showed that phosphate is only cleared from the plasma volume, and that it does not diffuse from red blood cells to plasma during the short time lapse of blood transit through the hemodialyzer [40].

Thus, for practical purposes, PO_4 behaves like a MM. Although the molecular weight of PO_4 is only 96 Da, because of the hydration shell, its effective "diffusive" molecular weight is more like 350 Da. Therefore, a simple guide to a truly adequate dose of dialysis may become that amount needed to control serum PO_4 without the need for dietary phosphate binders.

It is an interesting coincidence that the dialytic removal of PO_4 has now become an important goal in itself [41,42]. That is because elevated PO_4 may be an "accelerator" [43,44] of atherosclerosis in renal patients by causing arterial wall and atherosclerotic plaque calcifications [45].

Every-other-day dialysis (EODD)

As Kjellstrand pointed out, nothing could be more unphysiologic than 3×/week dialysis [46], the schedule that became the best available compromise in the early Seattle experience back in the 1960s.

Unless a dialysis center can run an 8-hour overnight schedule, as practiced in Tassin [19], there is no possible way to deliver an adequate dose of dialysis on a 3×/week schedule. This is especially true with the so-called standard 3- to 4-hour 3×/week schedule used for the vast majority of dialysis patients in the world today. No one can predict how this dilemma will be resolved over time. However, one compromise that, if implemented, would represent a major step forward in terms of getting the dialysis dose much higher is EODD [47], a schedule already embraced by many home HD patients.

EODD offers several important advantages to patients who are willing to make the extra effort in order to substantially improve their life expectancies and well-being. First, as Bleyer *et al.* [48] pointed out, the most dangerous period in terms of an adverse event, such as a stroke or a myocardial infarction, is the day after an extra day off dialysis, usually a Monday or a Tuesday. Second, there is no question that, with EODD, there would be a vast improvement in the ability to control blood pressure because it would be easier to keep the extracellular volume under much better control [49,50]. And finally, because we do not yet understand the kinetics of toxic MM removal, EODD might increase the weekly transfer of MM's even more than predicted, based on the slight increase in weekly dialysis time. A practical suggestion for making EODD more acceptable to a society that lives by the 7-day week is to use a schedule that does not change the day of dialysis every week as was originally proposed, but increase the frequency of dialysis to 4×/week, for example, Monday, Tuesday, Thursday, Saturday; or Monday, Wednesday, Friday, Saturday.

Conclusion

We have presented here evidence that, in order to have sufficient HD to restore and maintain reasonable health and long survival, either dialysis time must be increased to 8 hours 3×/week or dialysis frequency must be increased to more than 3 dialyses per week. Anything less results in the retention of toxic MM's that cause the persistence of signs and symptoms of chronic uremia, including anorexia, chronic malnutrition, peripheral neuropathy, and poor rehabilitation.

Dialysis dose based on Kt/V_{urea} is too low to cure these signs and symptoms of uremia because it is based on the erroneous assumption that urea removal accurately reflects removal of other uremic toxins. New criteria for easily monitoring the dose of dialysis must be devised.

Controlling the serum phosphate level without binders is an immediately available guide. In addition, the Dialysis Index [1,49] could be updated and computerized, and become a useful criterion for comparing dialysis results. Recently, a measure of dialysis dose, the HD product, that patients can calculate themselves has also been proposed [51].

Since it is now firmly established that some important uremic toxins are MM's, investigation must now be undertaken to increase our knowledge of the kinetics of MM's during dialysis, and dialysis regimens and techniques that will result in adequate removal. Dialysis prescription can then be

tailored to the needs of the individual patient in a cost effective manner.

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