

Hemofiltration and the Middle Molecule

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Ingrid Ledebø [pp 178-182] has written an editorial review exploring hemofiltration (HF) and indicates that we should reexamine this modality in light of recent technical improvements to assess whether the reported clinical advantages, confirmed in recent controlled prospective studies, offer a persuasive case for revisiting this venerable technique, i.e., the redux hypothesis. As a participant in the early enthusiasm for HF, it is nice to see a revival of interest in this old therapeutic friend.

What follows is a personal (read opinionated) view of the current scientific environment surrounding routine dialytic treatment of end-stage renal disease (ESRD) to see if the changes in this information base support the redux hypothesis. The premise underlying the original work on HF was, of course, that there were middle molecules present in the plasma of the ESRD patient that were pathophysiologically important in causing the syndrome of uremia. I will confine my comments to information that was not available in 1967 [1] and appears to me to be particularly relevant to the redux hypothesis. I shall not explore putative benefits such as hemodynamic stability [2, 3] or quality of life.

Middle Molecules

In 1967 the substantial body of literature on β_2 -microglobulin (β_2 M) had not yet surfaced. The etiologic link between β_2 M and bone/joint disease is now part of the

common wisdom attending the uremic syndrome. That β_2 M is a toxic middle molecule is not in question. The generic question that uremic amyloid osteoarthropathy raises, is whether the improvement noted in the transport characteristics of conventional dialysis membranes renders the enhanced efficiency of convective removal of middle molecules moot? As noted by Colton and Lysaght [4], the changes in manufacturing techniques for conventional hemodialysis (HD) cellulosic membranes over the last 10 years have resulted in a potential doubling of their diffusive transport capability. One of the most advanced cellulosic membranes (cellulose triacetate) which would be expected, because of its open pore structure as well as its thin wall, to be maximally transporting of β_2 M, when operated in the HD mode, has not shown in clinical study that the amount removed per treatment approaches that removed when this membrane is employed for HF [Soltys P, Clark W, personal commun.]. Unfortunately, even the enhanced amount removed per week by HF remains less than the amount generated metabolically for this time period. Further, several researchers have suggested that simply improving removal of β_2 M, without returning time averaged plasma concentrations to normal, results in less morbidity from amyloid deposits [5, 6]. The important insight offered by β_2 M kinetics is that it may not be possible to normalize time-averaged plasma concentrations of middle molecules with the size and generation rate of β_2 M using only a conventional, thrice weekly treatment schedule.

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The appetite-suppressing middle molecular weight substance(s) [7] present in the ultrafiltrate of human uremic plasma provides a clear inferential link to the common observation of malnutrition in both patients maintained on HD and peritoneal dialysis [8, 9]. Animal studies showing a reduction in dietary intake, when the active component is injected intraperitoneally, are persuasive. While there is no prospective data on patients maintained on HF versus HD, work cited by Ledebro [her references 22, 23] supports a comparable nutritional status for patients on HF with an average Kt/V urea value that is below that for the control population maintained on HD, i.e., small molecular weight toxins, for which urea is surrogate, do not appear to limit appetite in these clinical experiments.

The presence of granulocyte inhibitory proteins of middle molecular weight [10, 11] in the plasma of the ESRD patient holds promise of explaining the common occurrence of death by infection in this population. While the etiologic link is again inferential, it provides an investigative direction with a well-defined end point to explore this common cause of death [12] in the ESRD population.

Pathophysiologic Events

The interesting work on the release of inflammatory cytokines during HD [13] had not yet been reported in 1976. The identification that complement mediated generation of interleukin-1 and tumor necrosis factor α , either through alternate pathway activation from exposure of plasma to the membrane or through back transport of bacterial byproducts present in the dialysate, is relevant for evaluating the clinical impact of membranes that are both more hydraulically permeable (high flux) and with a larger mean pore radius than, for example, cuprophane¹.

Several recent studies [14, 15] from the United States Renal Data System (USRDS) database have shown that the choice of membrane has a significant influence on the relative risk of death. With use of cuprophane as the reference standard, the combined data from modified cellulose (primarily cellulose mono- and diacetate, but not triacetate) and synthetic membrane (primarily polysulphone)

shows a 20% reduction in mortality. This is disconcerting when one is trying to decipher whether the improved survival is the result of the better clearance spectrum offered by the 'Starling's flow' convective clearance that occurs with highly water permeable membranes operated in an HD mode, or whether it is simply the move to a complement-kind membrane. Mono- and di-substituted cellulose carry an intermediate level of complement activation that is roughly midway between what is measured with the 'lead standard' (cuprophane) and the virtually negligible activation typical of polysulfone. Yet the figures comparing survival between these modified cellulose and polysulfone membrane are the same. Inferential interpretation of this and other retrospective studies suggest that it is complement activation rather than convective transport that is responsible for the difference. However, one cannot in good scientific conscience cast out the *redux* hypothesis in explanation until a confirmatory prospective study distinguishing between complement activation and solute flux is completed. It is a shame that analysis of the complement-kind cellulose triacetate membrane that has convective transport characteristics comparable to the polysulphone membrane does not significantly enter this analysis, as one would then be able to make the distinction between convective transport and biocompatibility, as assessed by complement activation, as they influence survival rate. This particular expansion in our knowledge base, i.e., the role of cytokine generation, has made the identification of benefit from a morbid/mortal perspective of using HF as a maintenance technique a good deal more difficult as it casts out prior work cited in support of an advantage for HF when cuprophane membrane was used as the control group.

Confirmatory Observations

There is a general confirmation of the presence and pathophysiologic importance of middle molecules in the recent retrospective modeling work of Leypoldt et al. [16]. They show for a large data subset (7,000 patients) obtained from the USRDS that there is a clear correlation between the death rate and the membrane manufacturer's reported vitamin B₁₂ (1,200 daltons) clearance number for the dialysis membrane used. It is unlikely that the data are skewed toward this correlation by the upswing in use of synthetic complement-kind membranes, as discussed above, as their data set is drawn from a 1990 sample when the cuprophane membrane was most commonly (70%) used.

¹ It should be understood that these two qualities are not required to occur simultaneously in a dialysis membrane but commonly do so for reasons that relate to the sensitivity of water flow rate to the mean pore radius of the membrane.

Secondly, general confirmation may be found in a comparison of the values of Kt/V urea achieved for hemofiltration and compared with HF that are very roughly normalized for 2-year survival [17]. This work points out that 2-year survival values of 95% for HF and 72% for HD occur at respective Kt/V urea values of 1.5/week HF and 3.6/week for HD, using a thrice weekly treatment schedule. Clearly, molecules in uremic plasma, other than urea, and solutes for which urea is surrogate are implicated in this observed difference.

In summary, the database validating the basic premise for which HF was developed is now significantly stronger

than it was in 1967. We still need, however, well-controlled prospective studies aimed at tightening the etiologic link between the uremic parameter, e.g., death from infection, and the time-averaged concentration of the uremic middle molecule in the plasma of ESRD patients, e.g., granulocyte inhibitory proteins when conventional HD therapy with complement-kind membranes is compared with HF.

It will surprise no one that, in conclusion, I agree with Dr. Ledebro in calling for a reexamination of HF for routine use in maintaining patients with ESRD as a potentially superior modality for 'laundering' uremic blood.

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