The ADEMEX Study: Make Haste Slowly

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For every therapeutic initiative in medicine, efficacy represents the balance between the health benefits and the risks of that treatment. In an environment of limited resources, the cost-effectiveness of the intervention is an essential additional consideration. For hemodialysis, there is general acceptance that a thrice weekly Kt/V > 1.2 provides adequate dialysis in a cost-effective manner without unduly restricting patient time. For patients on peritoneal dialysis, the optimal dose of this modality has been more difficult to define and is much more controversial. We clearly need to provide enough peritoneal dialysis treatment to optimize survival without unnecessary increases in dialysis volumes and/or exchanges that would diminish quality of life and increase the cost of treatment.

The ADEMEX study in this issue of the Journal concludes that currently recommended adequacy guidelines require more peritoneal dialysis than is necessary for acceptable patient survival. It will clearly delight those who have espoused a pragmatic approach, whether for economic or convenience reasons. On the other hand, it will be less well accepted by those who take a urea kinetic approach to peritoneal dialysis. Patients will be happier with a decreased burden of treatment, while the impact on those who supply peritoneal dialysate is unpredictable. Simpler treatment may increase with numbers of patients using peritoneal dialysis, but each patient will use less dialysate.

Which viewpoint is correct? It is purpose of this editorial to examine the details of the ADEMEX study in relation to urea kinetic theory and to the previous large observational studies of peritoneal dialysis adequacy.

The technique of continuous peritoneal dialysis, first proposed by Popovich et al. (1,2), was based on urea kinetic modeling of peritoneal transport. For an anuric 70-kg person, a 12-L drain volume per day would produce a weekly Kt/V of 2.0. Observational studies, using either univariate (3–5) or multivariate statistical analyses (6,7), suggested that a weekly Kt/V of 1.9 to 2.1 was associated with better patient survival than lower Kt/V values. The Canada-USA (CANUSA) study of incident patients (7) assumed that renal and peritoneal clearances were equivalent and additive with respect to clearance of small solutes. The relative risk (RR) of death was decreased to 0.94 with an increase of 0.1 in weekly Kt/V. On the basis of the Cox model statistical analyses and assuming replacement of diminishing renal function with increased peritoneal clearance, the predicted 2-yr survival of incident patients at a weekly Kt/V of 2.1 was 70%. This same survival was predicted for a creatinine clearance of 70 L/wk per 1.73m² (7). An Italian study of prevalent patients found no survival benefit with weekly Kt/V > 1.96 or with a creatinine clearance > 58 L/wk per 1.73m² (6).

The KDOQI recommendations in 2001 were a weekly Kt/V target of 2.0 (sum of renal and peritoneal clearances) and a creatinine clearance target of 60 L/wk per 1.73m² for those with high and high average peritoneal transport, while those with low and low average transport had a target of 50 L/wk per 1.73m². These recommendations were made on the basis of urea kinetics and observational studies (8).

The ADEMEX study is a randomized clinical trial that is designed to test the null hypothesis that increasing peritoneal clearance to the KDOQI targets is not associated with better survival than a standard regimen of 2 L of dialysate infused four times daily (9). Although this study could not be blinded, it is a well-designed multicenter trial with appropriate statistical analyses. The abstract concludes that there are no clear survival advantages obtained by the increases in peritoneal clearance within the ranges evaluated in this study.

Many will read only the abstract and conclude that peritoneal dialysis treatment can safely revert to the standard one-size-fits-all (four exchanges of 2 L each per day) prescription. Abstracts can influence clinical practice greatly, irrespective of the details in the manuscript. One can point to the example of the abstract for the National Cooperative Dialysis Study (NCDS), which includes the statement, “... but dialysis treatment time had no significant effects” (10). This was the justification for an unfortunate era of shortened hemodialysis times. This statement was made on the basis of an analysis with a P value of 0.06, indicating that dialysis time was not statistically significant and therefore not clinically important. Statements omitted from an abstract can also influence practice. In the ADEMEX study, there was no difference in patient survival between the control and the intervention group, but there was a statistically significant increase in the proportion of deaths due to uremia and fluid overload in the control group. Had this statement been included in the abstract, it would have counterbalanced the conclusion that there is no clear survival advantage obtained by increases in peritoneal small solute clearances.

Oral presentation of the ADEMEX study results at the International Society of Peritoneal Dialysis Meeting in Mon-
treat in June, 2001, generated press releases and endorsement of the study results before the formal peer review process had been completed. Before publication, the ADEMEX study has been quoted by thought leaders in dialysis as providing evidence that Kt/V is a flawed concept and that we should return to the middle molecule hypothesis to develop an alternative measurement for adequacy of dialysis (11).

Before accepting these prepublication comments, it would be prudent to examine the data very carefully. Although randomized controlled trials produce the highest level of evidence for clinical decision-making and for Clinical Practice Guidelines, the structure of the study should be subjected to a critical methodologic review.

The theme of this editorial will be the validity of the conclusions reached by the ADEMEX study. The three types of validity that will be addressed are internal, external, and face validity. The first addresses the extent to which the study deals with the biases that are inherent in any research design; the second addresses the generalizability of the results to other populations, and the third evaluates the congruence of the results with current understandings of pathophysiology and other publications addressing similar themes.

**Internal Validity**

The randomization produced groups with similar baseline demographic and clinical characteristics, and the patients were appropriately analyzed both by an intention-to-treat analysis and by an as-treated analysis. The authors concluded that increasing peritoneal dialysis dose to reach currently recommended DOQI adequacy targets had no clear survival advantage over a standard regimen of four 2-L exchanges per day. The probability of a type 2 error was 15% for a 30% reduction in mortality risk.

However, the subjects were a mixture of incident and prevalent dialysis patients. The prevalent patients represented 58% of the total, and these were equally distributed between intervention and the control groups. The prevalent patients represent a survivor cohort with a probable overrepresentation of low and low-average peritoneal transporters. Those with high and high-average transport are more likely to transfer to hemodialysis or to die than are those with lower peritoneal transport (12). The classic peritoneal equilibrium test (PET) was not performed. The dialysis adequacy and transport test (DATT) was used instead (13). In Mexico, comparison of the DATT with the PET showed correlation but not agreement (14). The $r^2$ value indicated that the DATT explained 49% of the variation in PET. The $\kappa$ coefficient for the four categories was good at 0.81 but had a wide 95% confidence interval from 0.67 to 0.93. A formal PET, especially in the prevalent patients, would have added to internal validity.

The primary outcome was death, and there was no difference between groups. There were 157 deaths in the control group and 159 in the intervention group. Deaths attributable to inadequacy of dialysis and fluid removal were higher in the control group. Congestive heart failure was responsible for 13.4% of deaths in the control group and 5.7% in the intervention group ($P < 0.05$). For uremia, hyperkalemia, and acidosis, the proportions of deaths were 12.2% and 5.1% in the control and intervention groups, respectively ($P < 0.05$). Other causes of death included ischemic heart disease, stroke, peritonitis, and other infections. These accounted for 74.4% and 89.2% in the control and intervention groups, respectively. The dropout rate for uremia was 5% in the control and 0% in the intervention group. The loss to follow-up was high, with 9.9% of the control group and 8.7% of the intervention group lost.

The analysis was an intention-to-treat analysis with follow-up continuing after transfer to hemodialysis or other peritoneal dialysis. The technique survival is stated to be equal by life table analysis. The proportion transferring to hemodialysis in each group is assumed equal. The analysis demonstrated no difference in patient survival between control and intervention groups for important clinical subgroups based on age, diabetic status, and serum albumin. The multivariate analysis showed no association of peritoneal clearance with survival, while the association with renal creatinine clearance was significant (RR, 0.89 per 10 L/wk greater creatinine clearance).

The first threat to the internal validity of the study is the possibility of bias introduced by prevalent patients with the consequent underrepresentation of those with high and high-average peritoneal transport. The low and low-average transporters have a better survival independent of renal and peritoneal clearances of small solutes (12).

A second threat is the higher death rate due to congestive heart failure and uremia in the control compared with the intervention group (25.6% versus 10.8%). The 5% dropout rate attributed to uremia in the control group compared with none in the intervention group is another indication that uremia and fluid overload were more common in the control group than the intervention group.

A third threat is the possibility that survival after transfer to hemodialysis was due to the timing of the transfer and the quality of the hemodialysis treatment received. The technique failure rates were reported as equal, but we do not have data on the timing and number of transfers and the proportion of deaths after transfer.

**External Validity**

The patients were younger than the CANUSA (7) patients (46.6 to 47.9 yr compared with 54.3 yr), but the intervention was equally ineffective when analyzed according to age older and younger than 50 yr. The mean weight of the patients was 65.4 to 67.0 kg compared with 67.8 kg in the CANUSA study (7). The US patients in the CANUSA study had a mean body surface area (BSA) of 1.80 m$^2$ compared with the Canadian mean of 1.74 and the ADEMEX mean of 1.68 to 1.70.

Heart disease was an exclusion criterion. The cohort studied had history of ischemic cardiac disease or stroke in 6.0% of the control and 4.6% of the intervention group. In contrast, the CANUSA study (7) had 22.9% with class III or IV congestive heart failure, 14.6% with myocardial infarction, and 23.4% with angina. Some 34% of Canadian participants had a history of cardiovascular disease compared with 42% of Americans (7).

The first threat to the external validity of the ADEMEX
study is the age of the patients. In general, one would expect better survival among younger patients.

The second threat is the very low prevalence of cardiovascular disease in the ADEMEX study. If a uremic environment accelerates cardiovascular disease, those with established disease might be more susceptible to those challenges than those without cardiovascular disease. The results of the study should be generalized cautiously to those with a history of cardiovascular disease.

Face Validity

The conclusion, expressed in the abstract, is that increasing peritoneal clearance to achieve levels recommended by DOQI does not improve survival. The data are consistent with the observations by Diaz-Buxo et al. (15) and Bargman et al. (16) that residual renal function is much more important to survival than is peritoneal dialysis.

On the other hand, is there any evidence to suggest that peritoneal clearance does have a positive effect on clinical outcomes? Among 122 anuric peritoneal dialysis patients, Bhaskaran et al. (17) reported a RR of death of 0.54 (0.26 to 1.13) for those with a weekly peritoneal Kt/V >1.85. The effect is clinically important; failure to achieve statistical significance is related to low statistical power. In a study of anuric Asian peritoneal dialysis patients (18) with a mean weekly peritoneal Kt/V of 1.72, an increase of 0.1 per week was associated with a decrease in RR to 0.94 (0.92 to 0.99).

The threat to face validity is that the increased peritoneal clearance has no effect on survival is inconsistent with hemodialysis-based urea kinetic data and with the data from studies on anuric peritoneal dialysis patients.

Summary

The authors of the ADEMEX study are to be congratulated for applying the most rigorous research design, the randomized clinical trial, to this important question.

The ADEMEX study results indicate that there is no improvement in patient survival when peritoneal clearance of small solutes is increased to the adequacy targets recommended by KDOQI. It is possible that the inclusion and exclusion criteria produced a population whose survival was less dependent on peritoneal clearance of small solutes than the general peritoneal dialysis population. These patients were younger and had less cardiac disease than patients in other studies and may have had an overrepresentation of low and low-average transporters as defined by PET. The better than anticipated survival rate is consistent with a healthier population. The authors correctly indicate that their results do not exclude a beneficial effect on survival if higher peritoneal clearances could be achieved with future technologies.

The increased proportion of deaths attributed to uremia and fluid overload in the control group is an indication that the increased peritoneal small solute clearance is not without value. This is reflected in the discussion, in which the authors state that the results should not encourage a sense of complacency in the prescription behavior but rather focus attention on adequacy of dialysis care rather than attaining a target level of small level clearance.

The assumption of equivalence of renal and peritoneal small solute clearance is probably incorrect. On the other hand, the suggestion that failure to demonstrate an association between increased peritoneal small solute clearance and a reduced relative risk of death indicates no effect of peritoneal clearance is equally incorrect. Determination of the relative value of renal and peritoneal clearances is a subject for further study, with the peritoneal component being defined according to the osmotic agent and biocompatibility.

The ADEMEX study should be reviewed promptly by KDOQI using established processes. Pending that review, practitioners should continue to provide the maximum peritoneal clearance of urea and creatinine tolerated comfortably by the patient. Failure to reach the previously defined guidelines for adequacy should be accompanied by an exploration for signs and symptoms of uremia or malnutrition. If there were no clinically important adverse findings, continuation on peritoneal dialysis without change in the peritoneal dialysis dose would be appropriate.

References


See related article, “Effects of Increased Peritoneal Clearances on Mortality Rates in Peritoneal Dialysis: ADEMEX, a Prospective, Randomized, Controlled Trial,” on pages 1307–1320.