

## The ADEMEX Study and Its Implications for Peritoneal Dialysis Adequacy

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### ABSTRACT

In an attempt to improve patient outcomes in peritoneal dialysis (PD), national organizations (such as the National Kidney Foundation Dialysis Outcomes Quality Initiative [NKF-DOQI] process) have formulated clinical practice guidelines based on clinical evidence available at the time of development. For “adequacy” of PD it was acknowledged that there was no prospective randomized interventional clinical trial that evaluated the effect of an increase in peritoneal clearance on outcome. The ADEMEX study is the first such study designed to do this. It was well done and adequately powered for the primary analysis. The study findings indicate that over the range of solute clearances studied, an increase in peritoneal clearance is not associated with an incremental improvement in patient outcome. However, it is noted that the cause of dropout was different between groups, with more dropout for “uremia” in the control group. There are also some

limitations in the generalizability of the results. First, the exclusion criteria were likely to exclude patients who were small in body size or were high transporters, patients with the highest relative risk of death. Second, although there was an increase in small solute clearance between control and intervention groups, there was not likely to be an increase in clearance of other potential uremic solutes such as middle molecules. Third, the study did not examine outcomes for patients on cyclical therapy. Nevertheless it was a provocative, well-run clinical study which does have implications for clinical practice. It confirms that one prescription does not fit all patients, that many patients below current NKF-DOQI targets for small solute clearance are likely to be adequately dialyzed, and provides evidence-based clinical information for national societies to consider when preparing for the next revision of their guidelines.

The National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) clinical practice guidelines for adequacy of peritoneal dialysis (PD) were first published in 1997 in an attempt to provide evidence-based guidelines for the provision of adequate PD (1). These guidelines developed recommendations for when to initiate dialysis, how and when to measure PD dose, and recommendations for providing an adequate dose of dialysis. They also identified areas of future research needs while acknowledging that many of the guidelines are opinion based.

In 1997 conventional wisdom (not “level 1” outcome evidence) dictated that more (in terms of solute clearance) was better. However, it was thought that there may have been a point where further increases in solute clearance were associated with little additive benefit in expected patient outcome while possibly having a negative impact on patient quality of life due to time spent on dialysis. With these principals in mind, the NKF-DOQI Peritoneal Dialysis Adequacy Work Group suggested that to ensure adequate small

solute clearance for the average continuous ambulatory PD (CAPD) patient (all transport types) one should strive to achieve a target total solute clearance of  $Kt/V \geq 2.0/\text{week}$ . These guidelines were developed with the tacit assumption that 1 unit of small solute clearance (in terms of  $Kt/V$ ) by residual renal function afforded the patient the same survival advantage as 1 unit of peritoneal clearance and they were therefore additive one for one. This was not proven and it was suggested that more data were needed.

Subsequent observational studies that examined the relationship between total small solute clearance and mortality rates tended to show that patient survival was directly correlated with residual renal, not peritoneal, clearance (2,3). The perceived need to deliver higher and higher total solute clearances increased the cost, burden of therapy, time spent on dialysis, and likelihood of patient burnout. It also increased the number of patients who were “underdialyzed” while on PD because they did not achieve the numerical adequacy targets. The net result was a possible adverse effect on PD as a therapy, despite a real attempt to improve patient outcomes. This trend occurred despite the fact that there was no prospective, randomized, interventional clinical trial examining the effects of increased peritoneal small solute clearance on patient outcomes. The ADEMEX trial (ADEquacy of PD in MEXico) was designed to answer this important question.

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## ADEMEX Study

### Study Design

The ADEMEX study was a prospective, randomized, controlled, clinical trial that enrolled 965 subjects in 24 centers (4); both incident and prevalent patients were recruited. The patients were assigned (1:1 ratio) to the intervention or control group. Subjects in the control group continued on their existing PD prescription ( $4 \times 2$  L exchanges/day) while the interventional group had their PD regimen modified to achieve a peritoneal alone creatinine clearance of greater than  $60 \text{ L/wk}/1.73 \text{ m}^2$ .

The study was originally powered at 80% to detect a 5% absolute difference in 1-year survival, or equivalently a 30% reduction in mortality rates. This was based on the following assumptions: a target sample of 800 patients (400/group) and a mortality rate in the control group of 23 deaths/100 patient-years.

Death was the primary endpoint of the study. Secondary endpoints were hospitalizations, therapy-related complications, correction of anemia, and effects on nutritional status. All primary analyses were performed using intent-to-treat analysis and life-table techniques with comparisons made on the basis of log rank testing.

### Results

There were no differences in baseline characteristics between groups; minimum follow-up was 2 years. By design, there was a large difference in peritoneal clearance between the groups that was maintained throughout the study ( $Kt/V_p = 1.62 \pm 0.01$  in the control group and  $2.13 \pm 0.01$  in the interventional group,  $p < 0.001$ ). There was no difference in survival between the groups in an intent-to-treat analysis with a relative risk of death (intervention/control) of 1.00 (95% confidence interval [CI] 0.80–1.24). Overall the control group exhibited a 1-year survival of 85.5% and a 2-year survival of 68.3%, while survival in the intervention group was similar (1 year, 83.9%; 2 years, 69.3%). Furthermore, there was no detectable difference in survival in subgroup analysis after adjustment for factors known to influence survival in patients on PD (age, diabetic status, serum albumin levels, normalized estimate of protein intake, and residual renal clearance).

### Significance of the Study

I feel the results of this study are clinically relevant. The ADEMEX study is the first prospective, randomized, controlled, interventional, clinical trial to examine the effect of an increase in peritoneal clearance on outcome (survival) in patients on PD. As mentioned above, many societies have formulated clinical practice guidelines for the adequacy of PD (5,6). These target total solute clearance goals were developed based on clinical evidence available at that time. It was acknowledged that there were methodologic problems with the clinical studies these guidelines were based on, that there were no

prospective randomized interventional trials, and that there were no data to support the recommended clinical practice of adding residual renal and peritoneal clearances together in a 1:1 ratio. The ADEMEX study was designed to address those key clinical issues. Approximately 50% of patients were defined as anephric (glomerular filtration rate [GFR]  $< 1 \text{ ml/min}$ ) at enrollment into the study. The average peritoneal-only  $Kt/V$  in the study groups reflected values commonly observed in clinical practice.

### Study Flaws and Limitations

#### Exclusion Criteria

One potential limitation has to do with the selection criteria. To be included one had to be on CAPD using four 2 L exchanges/day and have a peritoneal creatinine clearance of less than  $60 \text{ L/wk}/1.73 \text{ m}^2$  with or without residual renal function. On this PD prescription, patients with a creatinine clearance of less than  $60 \text{ L/wk}/1.73 \text{ m}^2$  would tend to be larger patients and would more likely be low, low-average, and high-average transporters on peritoneal equilibration testing (PET). In patients with the same absolute amount of solute removed per day (creatinine clearance in L/wk), the “normalized” clearance (creatinine clearance in  $\text{L/wk}/1.73 \text{ m}^2$ ) is likely to be less in larger patients than in smaller ones. While in the ADEMEX database there was no difference in the risk of death between tertiles of body weight over the range of solute clearances studied, most other databases suggest that larger patients have a survival advantage. So despite excellent randomization and no difference in baseline characteristics, the smallest patients, those with an increased relative risk, would have been excluded.

It is well appreciated that although there is little difference in weekly  $Kt/V$  between transport types in patients on four 2 L exchanges/day, there is a marked difference in creatinine clearances based on transport type. The higher the transport type, the higher the creatinine clearance, making it likely that high transporters would tend to be excluded from the study. While the ADEMEX study found no influence of baseline peritoneal transport type on relative risk, some (but not all) studies have shown a higher relative risk of death on CAPD for high transporters.

Thus the study may have excluded patients who were high transporters or of small size, patients at the highest risk of death. Though the number of patients excluded in each category is likely to be small, exclusion of these patients may influence the generalizability of the results.

#### Weight

The average weight of patients in the ADEMEX study was  $65.4 \pm 12.4 \text{ kg}$  in controls and  $67.0 \pm 13.8 \text{ kg}$  in the intervention group (body surface area [BSA] of  $1.68 \pm 0.18$  versus  $1.70 \pm 0.19 \text{ m}^2$ ). In contrast, the average weight is higher in North American patients (72 kg) (7). If there are any solutes (such as middle molecules; see below) that are dwell time or convective transport dependent rather than instilled volume dependent, then,

for the same drain volume, the “normalized” clearance of these will be higher in smaller (Mexican) patients than in larger (North American) patients. Again, this will not influence results, but may influence generalizability of observations or modification of existing guidelines.

### Small Versus Middle Molecule Clearance

Solute clearance by diffusion depends on both the concentration gradients and molecular weights of the solutes in question. Increasing the instilled volume per exchange increases small solute clearance (as demonstrated in the interventional group of ADEMEX). However, as long as there is 24 hr/day of peritoneal dwell, an increase in instilled volume per dwell yields little to no change in middle molecule clearance. Hence ADEMEX examined the effect of an increase in small solute, not middle molecule clearance.

### Anuric Patients

In a subgroup analysis it was shown that the presence of residual renal function (defined as a GFR > 1 ml/min) was associated with a decrease in the relative risk of death. However, there was no difference in outcome between the 270 anuric control patients and the 250 anuric interventional patients over the range of solute clearances observed in the ADEMEX study. It is possible that in the presence of anuria there is an effect of peritoneal clearance, but the reduction in relative risk over a 2-year period is less than 30% or the effect is manifested over a longer period of observation. In a review of outcomes in 140 anuric Chinese patients, a correlation between peritoneal clearance and outcome was noted. However, in that study at baseline, 42% of patients were on three 2 L exchanges/day, doses less than the control group in this study (8). Observations in a group of anuric Canadian patients with a range of solute clearances similar to that observed in the ADEMEX study showed no effect of peritoneal clearance on outcome (9).

### Cause of Dropout

The total number of deaths and the total number of dropouts between the control and interventional groups were similar; however, the reasons for dropout differed between the groups. More patients in the control group withdrew from the study because of “uremia” (24 in the control group versus none in the intervention group;  $p < 0.0001$ ). Conversely, more patients in the intervention group withdrew from the study because of intraperitoneal volume-related problems (17 versus 1 in the control group;  $p < 0.001$ ). When these patients were reclassified as a “death” and the relative risk reanalyzed, there was still no difference between the control and intervention groups in outcomes. While there was no difference in outcome over the range of solute clearances studied for the group as a whole, the data suggest that a “one size fits all” prescription is not appropriate and that one must still individualize patient prescriptions.

### What ADEMEX did not Evaluate

The ADEMEX study did not evaluate the effect of an increase in clearance of all molecular weight solutes on outcome. Increasing the PD dose from four 2 L exchanges/day to four 2.5 L exchanges/day is not likely to be associated with an increase in middle molecular weight solute clearance (such as  $\beta_2$ -microglobulin [ $\beta_2M$ ]). Multiple studies in both PD (10) and hemodialysis (HD) (11,12) have shown that residual renal clearance is the primary predictor of outcome. Why is that? Is it because the presence of significant residual renal clearance results in increased  $\beta_2M$  clearance, a better steady state of blood pressure (BP) and volume control, or better sodium removal?

The study did evaluate peritoneal ultrafiltration (UF), a predictor of survival in other studies (13). In the control group, peritoneal UF was  $0.83 \pm 0.03$  L/day, whereas it was  $0.97 \pm 0.05$  L/day in the intervention group ( $p < 0.05$ ), a difference of 0.14 L/day. The study protocol did not control (or measure) daily salt or fluid intake. So although there was slightly more peritoneal UF, we do not know if BP or salt and blood volume control was different between the groups.

It also did not study the role of intermittent forms of PD such as nightly intermittent peritoneal dialysis (NIPD) or continuous cyclic peritoneal dialysis (CCPD). Therefore we cannot extrapolate the results of this study to those therapies. One could argue, however, that the subgroup of patients in the intervention group that were prescribed three daytime exchanges and two overnight exchanges would essentially be the same therapy as patients on CCPD with a last bag fill and midday exchange; however, data on this subgroup were not reported. Today most incident PD patients are on some form of cycler therapy, so again, although the data are extremely important clinical evidence, the generalizability may be limited.

### Implications

As noted in the ADEMEX discussion, these data are consistent with those in the literature, which suggest that initially (at weekly total small solute clearances below those studied in ADEMEX), as one increases dialysis dose, there is an improvement in survival. However, at some point the curve flattens and, as one further increases the dose, there is little incremental improvement in short-term clinical outcome. I believe that the ADEMEX data help us answer some very important clinical questions.

1. Can we prescribe one dose of dialysis for all patients? No. The dose may depend on protein intake and there were more dropouts for “uremic” causes in the control group than in the intervention group.

2. Can we feel comfortable not transferring a patient on PD to HD if they are doing well, eating well with stable weight and albumin, who is below NKF-DOQI targets for small solute clearance? Yes. The ADEMEX data support this position, as do the 2000 NKF-DOQI

guidelines, which advise using clinical judgment when evaluating adequacy of an individual patients' dialysis prescription.

3. Will NKF-DOQI revise their guidelines? Perhaps. The committee must meet as a group and review all the recently published data to make a judgment; this is in progress.

4. Do we need different makers for "adequacy" of dialysis? Possibly. It seems that once a certain minimal amount of total small solute clearance is obtained there is little further incremental benefit of an increase in dialysis dose if it does not further enhance all functions of the native kidney (e.g., steady-state control of volume, electrolytes, and larger molecular weight toxins). I do not think we should discard small solute clearance ( $Kt/V$  or creatinine) as a yardstick for "adequacy"; rather we should consider it one of many and also address phosphorus control, sodium removal, volume and BP control, and clearance of middle molecules.

### Conclusion

The ADEMEX study was a well-designed and well-implemented clinical trial that evaluated the effect of an increase in peritoneal clearance on the relative risk of death in PD patients on CAPD in Mexico. It is consistent with other studies in the literature. Unfortunately, as is often the case, the findings go against conventional teaching—it answers some clinical questions, but raises others. The more we know, the more we don't know. Why? Is it a function of aging (CAPD is now more than 25 years old), quest for knowledge, maturity of the therapy, or the limitations of our scientific process? Our challenge is to interpret the facts we do know and apply them intelligently to our patient care practices so that we

optimize all aspects of our patients lives in a user-friendly, cost-effective way.

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