ARE ADEQUACY TARGETS FOR PERITONEAL DIALYSIS MEANINGFUL?

Ram Gokal

Manchester Royal Infirmary, Department of Renal Medicine, Manchester, England

Peritoneal dialysis has undergone considerable change since it was first used in managing end stage renal disease (ESRD) patients in the early 1960s. Its use then was predominantly as a holding procedure for hemodialysis, and as such, it was used in a very limited number of patients. With the introduction of continuous ambulatory peritoneal dialysis (CAPD) in 1976, the use of PD has increased dramatically, with a corresponding improvement in survival rates as well retention on therapy (1,2). However, comparison of populations on PD and hemodialysis (HD) show that technique survival on PD is not as good as that on HD (3), and one of the major reasons is inadequate dialysis in up to 25% of patients.

Adequacy of dialysis should refer to providing enough replacement renal function to alleviate uremic symptoms and to improve a patient’s overall wellbeing and survival. Hitherto, adequacy of PD has come to be equated solely to solute removal, for which various groups have laid down guidelines and targets (4-6). Still, the best way to assess overall adequacy in peritoneal dialysis remains ill defined. Other aspects that need to be considered, in addition to solute removal, are adequate fluid removal, blood-pressure control, normal mineral metabolism [β2-microglobulin, parathyroid hormone (PTH), phosphate], and adequate nutritional status without acidosis, anemia, or lipid abnormalities.

DEFINING ADEQUATE SOLUTE REMOVAL

The measurement of dialytic dose in PD has traditionally been assessed in terms of weekly Kt/V urea and creatinine clearance normalized to body surface area. Solute clearance is an important predictor of good clinical outcome, but it should not be the only criteria used to assess adequacy of PD.

KEY WORDS: Adequacy; solute removal; nutrition; outcomes.

Correspondence to: R. Gokal, Consultant Nephrologist, Department of Renal Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL United Kingdom.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solute Clearance Guidelines by Various Groups for CAPD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total Kt/V urea</th>
<th>Total creatinine clearance (L/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Association UK (6) Minimum targets</td>
<td>&gt;1.7</td>
<td>&gt;50</td>
</tr>
<tr>
<td>NKF - DOQI Guidelines (4)</td>
<td>&gt;2.0</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Ad Hoc Committee (5) Underdialysis</td>
<td>&lt;1.7</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Borderline</td>
<td>1.7–1.89</td>
<td>50–59</td>
</tr>
<tr>
<td>Acceptable</td>
<td>1.9–2.09</td>
<td>60–69</td>
</tr>
<tr>
<td>Desirable</td>
<td>&gt;2.09</td>
<td>&gt;70</td>
</tr>
</tbody>
</table>
The issue therefore is not so much whether targets are relevant -indeed they are. However, they can only be meaningful if one can logically answer the question: "How much dialysis is enough?"

There is a need to assess what level of solute clearance will impact favorably on PD outcomes, what the relevant evidence is, and whether such levels can be achieved. One has, therefore, to balance the increased cost and inconvenience to patients of achieving the guidelines against the added benefit that would be derived from reaching the guidelines.

It seems that current guidelines and targets, especially DOQI guidelines, are set on total clearance values, and the evidence that these clearances affect outcome is indirect. Targets may need to be higher (as advocated in DOQI guidelines), but evidence for this is limited. Some low limit - for example, Kt/V urea less than 1.9 per week -is prudent to have, but we should not fool ourselves into believing that these limits are validated.

DELIVERED DIALYSIS DOSE AND PATIENT SURVIVAL

Five cohort studies have related patient survival and delivered PD dose measured by Kt/V urea. De Alvaro et al (8) showed that patients with a Kt/V urea of 2 per week had a better survival rate than those with a Kt/V urea of 1.7 per week. Blake et al (9) found that a Kt/V urea of less than 1.5 per week was associated with an increased risk of death. Genestier et al (10) suggested that a Kt/V urea of greater than 1.7 per week improved survival, whereas Maiorca et al (11) found that a Kt/V urea of greater than 1.96 per week was associated with a better survival. Teehan et al (12) showed that a Kt/V greater than 1.89 per week was associated with a decreased risk of death. These were all univariate analyses and did not include confounding comorbidities.

The CANUSA study (13) included comorbidities and showed that a decrease of 0.1 per week in Kt/V urea was associated with a 5% increase in the relative risk of death. The CANUSA study predicted a 75% survival at two years with a sustained Kt/V urea of 2 per week. Many studies have shown that survival is enhanced by a larger delivered PD dose, and the targets determined by the theoretical constructs are certainly in proximity to the clinical results desired. We could therefore say that strong evidence is available to support the concept that a delivered Kt/V urea of greater than 1.7 per week improves mortality outcomes. Where the level should be set to maximize outcome is still unproved, but is likely to fall in the region of 1.9 -2 per week.

It is important to realize that the CANUSA study was an observational cohort and not an interventional or randomized controlled study. It identified associations and made predictions, but no cause and effect relationship is implied. In addition, 75% of the deaths in the first two years were cardiovascular in nature; some concern exists regarding whether increasing the target dose would necessarily impact on this. One must be cautious to avoid over-interpreting the CANUSA results.

Furthermore, the existing literature is completely confounded by residual renal function and peritoneal transport permeability (7). No study has yet clearly shown that a prospective increase in peritoneal clearance leads to improved outcome. The exact relationship between PD clearance and outcomes remains undefined. Hence, the DOQI guidelines on solute clearance may arguably be regarded as "opinion-based" rather than "evidence-based". Furthermore, concern exists that these targets may be difficult to achieve in large patients who are devoid of residual renal function (14,15) and that the dialysis modality may be changed unnecessarily from CAPD to automated PD or to HD on the basis of inability to obtain these targets.

The data from outside the U.S. suggests that, compared to HD, PD patients have been doing relatively well with standard prescriptions that almost certainly do not achieve the DOQI targets (16); successful outcomes are seen in the Far East where many patients perform only three exchanges per day. This observation suggests that a more aggressive policy may not be absolutely essential to obtain good results. Furthermore, the size of the patient does not appear to be related to outcome (17,18).

Overall, therefore, the absolute minimum level of solute clearance should be 1.7 per week Kt/V urea and 50 L/week/1.73 m2 creatinine. Anything below that is clearly unacceptable. Higher targets are certainly desirable and should be aimed for whenever possible. The higher target values should be applied with knowledge, forethought, and in conjunction with other broader-based areas of adequacy.

DIALYSIS DOSE AND NUTRITION

Limited, inconclusive data link dialysis dose and nutritional outcomes. Most studies are cross-sectional, and positive correlation between PD dose and serum albumin concentration has been demonstrated in only two studies (19,20). In contrast, most found no correlation or an inverse correlation (21-24). Even in longitudinal studies of dialysis adequacy and body composition as measured by anthropometry, DEXA (dual energy x-ray absorptiometry), or creatinine kinetics, there was no correlation with serum albumin concentration (22,24).
The DOQI guidelines posited a link between nutrition and PD dose as measured by small-solute clearance. Urea production is related to protein intake and degradation. The rationale for the link is based on the finding that urea production is correlated with dietary protein intake and that the former provides a reasonable approximation of the latter. However, the relationship arose from the observed cross-sectional correlation between PD dose (Kt/V urea) and protein intake [extrapolated from a normalized protein catabolic rate (nPCR) or a normalized protein equivalent of nitrogen appearance (nPNA)].

The strength of this correlation (most values are in the region of r = 0.5 -0.6) led to the conclusion that urea clearance is an important determinant of PNA and that increasing the dialysis dose will increase dietary protein intake. This approach is flawed by the phenomenon of mathematical coupling (25,26) -namely that the two variables owe part of their relationship to a common component. Indeed, a relationship may well exist between nutrition and solute clearance. However, the relationship cannot be proved using the cross-sectional analysis. Prospective studies that directly measure dietary protein intake need to be undertaken to prove the relationship.

Five studies address the problem (27-31). Two studies have shown an increase and three did not. Most did not assess dietary protein intake. None of the studies shows a change in serum albumin concentration. In several of the studies, the increase in dialysate volume was counterbalanced by a spontaneous, gradual decrease in residual renal function, resulting in no change in solute removal as assessed by small-solute clearance. It may be that the increase in solute clearance achieved in these studies is not sufficient to have an impact on dietary protein intake. What has clearly been shown is that residual renal function affects nutritional status, and decline in residual renal function leads to a decrease in protein intake (32).

CONCLUSION

Overall, targets of solute clearance are indeed important, and a clear indication exists that low solute clearances (less than 1.7 per week Kt/V urea and less than 50 L/week creatinine) are indeed harmful.

The optimal solute clearance level is still undefined, but may well be in the region of 1.9 -2 per week Kt/V urea and 55 -60 L/week creatinine; these targets should be aimed for. Evidence that solute clearance impacts on nutrition is still not readily available, and further prospective studies need to be done to delineate the optimum level of solute clearance to maximize morbidity, mortality, and nutritional status.

REFERENCES

15. Tzamaloukas AH, Dimitriadis A, Murata GH,


