The rise and fall of the $K_t/V$ concept in CAPD

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Introduction

A simple figure to quantify the dialysis dose is attractive by all means. It facilitates the dialysis prescription and allows to study effects of the dialysis dose on outcome. $K_t/V_{urea}$ as developed by Gotch et al. for haemodialysis, meets this requirement because essentially it means that large patients need more dialysis, either by a higher urea clearance or by a longer treatment time, than small patients do [1]. The disadvantage of $K_t/V_{urea}$ is that only the clearance of urea is taken into account, one of the smallest uraemic toxins, while no attention is paid to the removal of the so-called ‘middle-molecules’ and of excess of body fluid.

Peritoneal dialysis is different from haemodialysis, because the peritoneal clearance of low molecular weight solutes is much lower than in haemodialysis while that of middle-molecules is higher. For instance, the average peritoneal urea clearance in CAPD is 7 ml/min, which is about half of that delivered on a weekly basis by haemodialysis. However, the peritoneal clearance of β2-microglobulin ranges between 0.4 and 1.3 ml/min [2]. These values are much higher than those achieved by conventional haemodialysis [3]. Nevertheless urea kinetic modelling has also been advocated for the assessment of adequacy in CAPD [4].

In this comment the first retrospective studies on $K_t/V_{urea}$ in peritoneal dialysis will be discussed, followed by prospective cohort studies and studies in anuric peritoneal dialysis patients. Finally these studies will be compared to those obtained in a randomized controlled trial.

Retrospective studies

A relationship between total $K_t/V_{urea}$, i.e. peritoneal and renal, has been reported in some retrospective studies [5–7], but not in all of them [8]. In none of these studies peritoneal $K_t/V_{urea}$ was analysed separately, despite the observation, done in a number of studies, showing that renal $K_t/V_{urea}$ or residual urea clearance had a large contribution to total $K_t/V_{urea}$ [9,10].

Prospective cohort studies

The first prospective cohort study by Blake et al. was unable to find an effect of total $K_t/V_{urea}$ on patient survival [11]. However, this study has been criticized for using a fixed percentage of body weight to assess the volume of distribution of urea ($V$). After reanalysis of the data using Watson’s formula to estimate $V$, it appeared that a significant excess of deaths was present when total $K_t/V_{urea}$ was <1.5 per week [12]. In accordance, $K_t/V_{urea}$ at 6 months was a significant risk factor for death, but this could entirely be explained by the impact of residual renal function [13]. A similar result was reported in the study of Szeto et al. from Hong Kong [14] and in that of Rocco et al. from the US [15]. However, in a prospective multicenter study in new peritoneal dialysis patients, $K_t/V_{urea}$ at 3 months was not a significant risk factor of death after correction for co-morbidity [16].

The CANUSA study, performed in 14 dialysis centres in the US and Canada, is a prospective cohort study in 680 incident continuous peritoneal dialysis patients [17]. The inclusion period comprised 3.3 years, the mean follow-up per patient was 1.2 years. Mean $K_t/V_{urea}$ at entry was 2.38 per week and had decreased to 1.99 after 2 years. Multivariate analysis showed a 6% reduction of the relative mortality risk for every 0.1 increase in $K_t/V_{urea}$ per week. In particular, these results were the basis for the recommendations made by the peritoneal dialysis adequacy work group of the National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) on the minimum dose for adequate peritoneal dialysis [18]. The working group considered a $K_t/V_{urea}$ of 2.0 per week, an evidence based minimum for adequate CAPD. In the presence of residual renal function peritoneal and renal $K_t/V_{urea}$ could be added up, in the absence of residual renal function the target had to be reached by peritoneal clearance only. This recommendation created much uncertainty among nephrologists treating patients with CAPD, because the average peritoneal $K_t/V_{urea}$ on the conventional 4×2.1 prescription is ~1.7 per week in most patients. Higher values can only be reached by increasing the volume and/or the
number of exchanges, both of which will reduce the attraction of CAPD for patients.

How solid is the evidence?

Criticisms can be raised concerning two items. The first criticism regards the assumption that renal and peritoneal urea clearance are equivalent with regard to control of uremic morbidity. This has not been validated by the working group. From a theoretical point of view the equivalency concept is debatable because renal function includes not only glomurular filtration but also tubular secretion and reabsorption, as well as various endocrine functions. Tubular secretion is especially important in the removal of organic acids. In the recent study of Jansen et al. the relationship between \( K_t/V_{\text{urea}} \) and the normalized protein equivalent of nitrogen appearance was markedly different between predialysis patients and anuric PD patients [19]. The results suggested that with a \( K_t/V_{\text{urea}} \) of 2.0 per week predialysis patients had a higher dietary protein intake than anuric PD patients.

The possibilities of influencing the decline of residual renal function are limited. To answer the question of whether this can be compensated for by increasing the peritoneal removal of urea requires an analysis of possible effects of peritoneal \( K_t/V_{\text{urea}} \) on patient survival. Up to now no prospective cohort study has been able to show a relationship between peritoneal \( K_t/V_{\text{urea}} \) and mortality [14–16]. Moreover, a recent reanalysis of the CANUSA data revealed that only renal \( K_t/V_{\text{urea}} \) and not peritoneal \( K_t/V_{\text{urea}} \) predicted outcome [20]. The effect of peritoneal \( K_t/V_{\text{urea}} \) on outcome is best studied in anuric PD patients. In three out of four studies no association between \( K_t/V_{\text{urea}} \) and mortality was found [21–23]. Only the study by Szeto et al. reported an effect of \( K_t/V_{\text{urea}} \) on patient survival [24]. However, this study has some special features, such as the practice of a 3 × 2 l regimen in most patients, the use of the last \( K_t/V_{\text{urea}} \) measurement before death, and the fact that death after conversion to haemodialysis was counted as an event without taking a time restriction into account. Based on all these cohort studies it can be concluded that the bulk of evidence suggests that the association between \( K_t/V_{\text{urea}} \) and survival can be attributed to the renal and not to the peritoneal component.

The second criticism is that peritoneal transport status, as determined with the peritoneal equilibration test, has not been taken into consideration. The presence of a ‘high’ or better ‘fast’ peritoneal transport status has been associated with an excess mortality [25] and with a lower combined patient and technique survival compared to the other transport groups [26]. These fast transporters often have poor ultrafiltration rates and are therefore at risk of overhydration. As peritoneal \( K_t/V_{\text{urea}} \) is mainly determined by the drained dialysate volume, this patient category is also likely to have a low peritoneal \( K_t/V_{\text{urea}} \). Given the high cardiovascular mortality rates in dialysis patients, the effect of a fast transporter status is more likely to be dependent on the hydration status than on insufficient removal of urea. Recently, an over-representation of a fast peritoneal transport status in patients with severe co-morbidity has been reported [27,28]. This is in line with the relationship between the presence of a fast peritoneal transport status and a low serum albumin at the start of dialysis, because albumin can be considered to reflect the severity of co-morbidity. This relationship has been reported in a number of studies (for an example see [29]). Taking all these findings together, it may well be that pre-existent co-morbidity contributes to the observed relationship between \( K_t/V_{\text{urea}} \) and outcome.

The ADEMEX study

The question of whether an increase in the dose of peritoneal dialysis to the DOQI targets improves patient survival can only be answered in a randomized controlled trial. The recently published ADEMEX study [30] is the only study in which 965 prevalent and incident CAPD patients from 24 dialysis centres in Mexico, who had a peritoneal creatinine clearance of < 60 l/week/1.73 m², were randomized into a control and a treated group. The control group was treated with CAPD, 4 × 2 l. The dialysis dose was increased in the treated group mainly by increasing the volume per exchange, to reach the target of a peritoneal creatinine clearance of 60 l/week/1.73 m². During the follow-up of 2 years both \( K_t/V_{\text{urea}} \) and creatinine clearance were markedly different between the two groups. Mean peritoneal \( K_t/V_{\text{urea}} \) exceeded 2.0 per week at all months during the 2-year period. However, no differences between the two groups were found for patient survival, patient survival in anuric patients, technique survival and combined patient and technique survival. Also no differences were present for the number of hospital admissions, the number of hospital days, peritonitis incidence and exit-site infections. The mean number of hernia’s was 7.1 per 100 patients in the control group and 10.6 in the treated group but this difference was not significant.

Conclusion

Peritoneal \( K_t/V_{\text{urea}} \) is a convenient way to express the removal of urea by peritoneal dialysis. For assessment of adequacy of peritoneal dialysis other factors such as hypertension and volume status should also be taken into account. The DOQI target of a \( K_t/V_{\text{urea}} \) of 2.0 per week is not based on evidence, but merely on statistical relationships in observational studies. By definition these studies can never show cause effect relations. The results of the ADEMEX study provide no evidence that a peritoneal \( K_t/V_{\text{urea}} \) of 2.0 per week is better than 1.7. It can therefore be concluded that the majority of
PD patients can safely be treated with the conventional CAPD prescription of 4 × 2 l. However, periodic assessment of peritoneal function and adequacy of the dialysis prescription should be performed in all patients. This should include both clinical and clearance assessments.

References